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=> s thr or f2r or (coagulation factor II receptor) or (thrombin receptor) or
(par()1) or (hpar()1)
L1         82751 THR OR F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN
                 RECEPTOR) OR (PAR(W) 1) OR (HPAR(W) 1)

=> s l1 and (antisense or ribozyme or triplex)
   5 FILES SEARCHED...
L2          8539 L1 AND (ANTISENSE OR RIBOZYME OR TRIPLEX)

=> s l1 (p) (antisense or ribozyme or triplex)
L3           587 L1 (P) (ANTISENSE OR RIBOZYME OR TRIPLEX)

=> s f2r or (coagulation factor II receptor) or (thrombin receptor) or (par()1) or
(hpar()1)
L4          7436 F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN RECEPTOR)
                 OR (PAR(W) 1) OR (HPAR(W) 1)

=> s l4 and (antisense or ribozyme or triplex)
L5           272 L4 AND (ANTISENSE OR RIBOZYME OR TRIPLEX)

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6           212 DUP REM L5 (60 DUPLICATES REMOVED)

=> s l6 and PY<2000
   3 FILES SEARCHED...
L7            83 L6 AND PY<2000

=> d l7 ibib abs 1-30

L7   ANSWER 1 OF 83      MEDLINE
ACCESSION NUMBER:    2001670639      MEDLINE
DOCUMENT NUMBER:     21572906   PubMed ID: 11715477
TITLE:               The inhibiting effect of antisense
                     thrombin receptor gene on the
                     proliferation of pig vascular smooth muscle cell.
AUTHOR:              Zhang Q; Jiang Y; Liu D
CORPORATE SOURCE:    Cardiovascular Institute and Fu Wai Hospital, Chinese
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	Academy of Medical Sciences and Peking Union Medical College, Beijing 100037.
SOURCE:	CHUNG-HUA I HSUEH TSA CHIH [CHINESE MEDICAL JOURNAL], **(1999 May)** 79 (5) 365-8. Journal code: 7511141. ISSN: 0376-2491.
PUB. COUNTRY:	China
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	Chinese
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200112
ENTRY DATE:	Entered STN: 20011122 Last Updated on STN: 20020123 Entered Medline: 20011221

AB OBJECTIVE: To search for an effective approach to prevent the formation of restenosis after angioplasty. METHODS: A recombinant eukaryotic expression plasmid vector containing partial **antisense thrombin receptor** (ATR) gene named pcDNA3/ATR was constructed using recombinant DNA technique. Mini-pig aorta injury model was established by over-sized balloon catheter combined with high cholesterol diet feeding and its aortic smooth muscle cells(ASMC) were cultured. The effect of ATR gene expression in mini pig ASMC proliferation and growth factor gene expression were studied by 3H-TdR incorporation and Northern blot. RESULTS: The DNA synthesis in pig ASMC could be inhibited by ATR gene expression (The DNA synthesis in normal ASMC was lowered by 41.8%, and that in ASMC from injured artery was lowered by (50.3%). The mRNA and protein synthesis of TR could be down regulated by ATR gene expression. The mRNA expression of PDGF-A chain and bFGF stimulated by fetal calf serum (FCS) with thrombin were both downregulated in pig ASMC with expressed ATR gene. CONCLUSION: ATR gene expression can inhibit the proliferation of pig ASMC, and this is induced by its inhibiting effect on TR and finaly the signal transduction in ASMC.

L7 ANSWER 2 OF 83	MEDLINE
ACCESSION NUMBER:	1999025943 MEDLINE
DOCUMENT NUMBER:	99025943 PubMed ID: 9808563
TITLE:	Protease-activated receptor 1 (**PAR-1**) is required and rate-limiting for thrombin-enhanced experimental pulmonary metastasis.
AUTHOR:	Nierodzik M L; Chen K; Takeshita K; Li J J; Huang Y Q; Feng X S; D'Andrea M R; Andrade-Gordon P; Karpatkin S
CORPORATE SOURCE:	New York University Medical Center and Kaplan Cancer Center, New York, NY, USA.
SOURCE:	BLOOD, **(1998 Nov 15)** 92 (10) 3694-700. Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:	199812
ENTRY DATE:	Entered STN: 19990115 Last Updated on STN: 19990115 Entered Medline: 19981221

AB Thrombin-treated tumor cells induce a metastatic phenotype in experimental pulmonary murine metastasis. Thrombin binds to a unique protease-activated receptor (**PAR-1**) that requires N-terminal proteolytic cleavage for activation by its tethered end. A 14-mer **thrombin receptor** activation peptide (TRAP) of the tethered end induces the same cellular changes as thrombin. Four murine tumor cells (Lewis lung, CT26 colon CA, B16F10 melanoma, and CCL163 fibroblasts) contain **PAR-1**, as detected by reverse transcriptase-polymerase chain reaction (RT-PCR). B16F10 cells did not contain the two other thrombin receptors, PAR-3 and glycoprotein Ib. TRAP-treated B16F10 tumor cells enhance pulmonary metastasis 41- to 48-fold (n = 17). Thrombin-treated B16F10 cells transfected with full-length murine

PAR-1 sense cDNA (S6, S7, S14, and S22) enhanced their adhesion to fibronectin 1.5- to 2.4-fold (n = 5, P <.04), whereas thrombin-treated wild-type cells do not. S6 (adhesion index, 1.5-fold) and S14 (index, 2.4-fold) when examined by RT-PCR and Northern analysis showed minimal expression of **PAR-1** for S6 over wild-type and considerable expression for S14. Immunohistochemistry showed greater expression of **PAR-1** for S14 compared with wild-type or empty-plasmid transfected cells. In vivo experiments with the thrombin-treated S14 transfectant showed a fivefold to sixfold increase in metastases compared with empty-plasmid transfected thrombin-treated naive cells or S6 cells (n = 20, P =.0001 to .02). **Antisense** had no effect on thrombin-stimulated tumor mass. Thus, **PAR-1** ligation and expression enhances and regulates tumor metastasis.

L7 ANSWER 3 OF 83 MEDLINE
ACCESSION NUMBER: 1998364972 MEDLINE
DOCUMENT NUMBER: 98364972 PubMed ID: 9701242
TITLE: **Thrombin receptor** overexpression in malignant and physiological invasion processes.
AUTHOR: Even-Ram S; Uziely B; Cohen P; Grisaru-Granovsky S; Maoz M; Ginzburg Y; Reich R; Vlodavsky I; Bar-Shavit R
CORPORATE SOURCE: Department of Oncology, Hadassah-Hebrew University Hospital, Jerusalem, Israel.
SOURCE: NATURE MEDICINE, **(1998 Aug)** 4 (8) 909-14.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980903
Last Updated on STN: 19980903
Entered Medline: 19980825

AB Although the involvement of soluble and matrix-immobilized proteases in tumor cell invasion and metastasis is well recognized, the role of proteolytically activated cell surface receptors has not been elucidated. We report here that **thrombin receptor**, a member of the protease-activated receptor family, is preferentially expressed in highly metastatic human breast carcinoma cell lines and breast carcinoma biopsy specimens. Introduction of **thrombin receptor** **antisense** cDNA considerably inhibited the invasion of metastatic breast carcinoma cells in culture through a reconstituted basement membrane. During placental implantation of the human embryo, **thrombin receptor** is transiently expressed in the invading cytotrophoblasts. These results emphasize the involvement of **thrombin receptor** in cell invasion associated with tumor progression and normal embryonic development.

L7 ANSWER 4 OF 83 MEDLINE
ACCESSION NUMBER: 1998232195 MEDLINE
DOCUMENT NUMBER: 98232195 PubMed ID: 9572483
TITLE: Protein kinase C beta modulates thrombin-induced Ca2+ signaling and endothelial permeability increase.
AUTHOR: Vuong P T; Malik A B; Nagpala P G; Lum H
CORPORATE SOURCE: Department of Pharmacology, University of Illinois at Chicago, College of Medicine, 60607-7174, USA.
CONTRACT NUMBER: HL 27016 (NHLBI)
HL 45638 (NHLBI)
HL 46350 (NHLBI)
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, **(1998 Jun)** 175 (3) 379-87.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980529
Last Updated on STN: 19980529
Entered Medline: 19980515

AB We investigated the function of the Ca2+-dependent protein kinase C (PKC) beta1 in the regulation of endothelial barrier property. Human dermal microvascular endothelial cells (HMEC-1) were transduced with full-length PKCbeta1 **antisense** (AS) cDNA or control pLNCX vector to generate stable cell lines (HMEC-AS and HMEC-pLNCX, respectively). Analyses indicated that HMEC-AS expressed the **antisense** PKCbeta1 transcript with decreased PKCbeta protein level (without a change in PKCalpha or PKCepsilon). The baseline transendothelial 125I-albumin clearance rates of HMEC-1, HMEC-pLNCX, and HMEC-AS were 5.0+/-0.5 x 10(-2), 6.8+/-0.4 x 10(-2), and 6.9+/-0.6 x 10(-2) microl/min, respectively. Activation of HMEC-1 and HMEC-pLNCX with phorbol 12-myristate 13-acetate (PMA) increased the rates to the respective 14.5+/-1.7 x 10(-2) microl/min and 16.9+/-2.8 x 10(-2) microl/min (corresponding to 191% and 149% increases over baseline). However, in HMEC-AS, PMA increased the rate to 9.8+/-1.0 x 10(-2) microl/min (42%). When HMEC-1 and HMEC-pLNCX were activated with thrombin, the rates increased to 10.8+/-1.4 x 10(-2) and 14.0+/-1.9 x 10(-2) microl/min, respectively (116% and 106%). In contrast, thrombin stimulation of HMEC-AS more than doubled the increase to 27.2+/-3.5 x 10(-2) microl/min (294%). Furthermore, the thrombin-induced peak increase in the [Ca2+]i in HMEC-AS was greater than in control cells. Fluorescence-activated cell sorter analysis of **thrombin receptor** expression indicated that the augmented thrombin-induced responses were not attributable to altered receptor density in HMEC-AS. These results indicate that PKCbeta functions in a negative feedback manner to inactivate thrombin-generated signals and thereby modulates the endothelial permeability increase. Because decreased PKCbeta expression significantly reduced the PMA-induced permeability increase, PKCbeta may downregulate **thrombin receptor** function upstream of PKC activation (i.e., Ca2+).

L7 ANSWER 5 OF 83 MEDLINE
ACCESSION NUMBER: 1998147082 MEDLINE
DOCUMENT NUMBER: 98147082 PubMed ID: 9486128
TITLE: Protein kinase C beta regulates heterologous desensitization of **thrombin receptor** (**PAR-1**) in endothelial cells.
AUTHOR: Yan W; Tiruppathi C; Lum H; Qiao R; Malik A B
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, University of Illinois, Chicago 60612, USA.
CONTRACT NUMBER: HL-27016 (NHLBI)
HL-45638 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1998 Feb)** 274 (2 Pt 1) C387-95.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980407
Last Updated on STN: 19980407
Entered Medline: 19980323

AB We studied the effects of protein kinase C (PKC) activation on endothelial cell surface expression and function of the proteolytically activated **thrombin receptor** 1 (**PAR-1**). Cell surface **PAR-1** expression was assessed by immunofluorescence (using anti-**PAR-1** monoclonal antibody), and receptor activation was assessed by measuring increases in

cytosolic Ca2+ concentration in human dermal microvascular endothelial cells (HMEC) exposed to alpha-thrombin or phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA). Immunofluorescence showed that thrombin and TPA reduced the cell surface expression of **PAR-1**. Prior exposure of HMEC to thrombin for 5 min desensitized the cells to thrombin, indicating homologous **PAR-1** desensitization. In contrast, prior activation of PKC with TPA produced desensitization to thrombin and histamine, indicating heterologous **PAR-1** desensitization. Treatment of cells with staurosporine, a PKC inhibitor, fully prevented heterologous desensitization, whereas thrombin-induced homologous desensitization persisted. Depletion of PKC beta isozymes (PKC beta I and PKC beta II) by transducing cells with **antisense** cDNA of PKC beta I prevented the TPA-induced decrease in cell surface **PAR-1** expression and restored approximately 60% of the cytosolic Ca2+ signal in response to thrombin. In contrast, depletion of PKC beta isozymes did not affect the loss of cell surface **PAR-1** and induction of homologous **PAR-1** desensitization by thrombin. Therefore, homologous **PAR-1** desensitization by thrombin occurs independently of PKC beta isozymes, whereas the PKC beta-activated pathway is important in signaling heterologous **PAR-1** desensitization in endothelial cells.

L7 ANSWER 6 OF 83 MEDLINE
ACCESSION NUMBER: 97330161 MEDLINE
DOCUMENT NUMBER: 97330161 PubMed ID: 9186620
TITLE: Thrombin activates NF-kappa B through **thrombin receptor** and results in proliferation of vascular smooth muscle cells: role of thrombin in atherosclerosis and restenosis.
AUTHOR: Maruyama I; Shigeta K; Miyahara H; Nakajima T; Shin H; Ide S; Kitajima I
CORPORATE SOURCE: Department of Laboratory Medicine, Faculty of Medicine, University of Kagoshima, Japan.
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, **(1997 Apr 15)** 811 429-36.
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970721
Last Updated on STN: 19970721
Entered Medline: 19970708

AB We investigated the role of thrombin in the pathogenesis in atherosclerosis and restenosis. First we examined the effect of thrombin on cultured human vascular smooth muscle cells (VSMC). We showed that thrombin acts as a mitogen on VSMC through **thrombin receptor**. The expression of **thrombin receptor** was increased in the cell lines of VSMC established from directional coronary atherectomy (DCA). This is more pronounced in the cells from patients with restenosis after PTCA. Next we investigated the signaling pathway from thrombin/**thrombin receptor**. Thrombin activates **thrombin receptor** resulting in the exposing of the agonist peptide domain (**thrombin receptor** agonist peptide, TRAP). The signal from thrombin/**thrombin receptor** activated protein C kinase, tyrosine kinase, and MAP kinase and resulted in NF-kappa B activation. Furthermore, treatment of the cells with **antisense** p65 oligodeoxynucleotides of NF-kappa B inhibited the thrombin-stimulated growth of VSMC in vitro. These results suggest that thrombin may have a role in the pathogenesis of atherosclerosis and restenosis after PTCA through the **thrombin receptor**.

L7 ANSWER 7 OF 83 MEDLINE
ACCESSION NUMBER: 97307623 MEDLINE
DOCUMENT NUMBER: 97307623 PubMed ID: 9164965
TITLE: Thrombin induces endothelial type II activation in vitro: IL-1 and TNF-alpha-independent IL-8 secretion and E-selectin expression.
AUTHOR: Kaplanski G; Fabrigoule M; Boulay V; Dinarello C A; Bongrand P; Kaplanski S; Farnarier C
CORPORATE SOURCE: Laboratory of Immunology, INSERM Unit 387, Hospital Sainte Marguerite, Marseille, France.
CONTRACT NUMBER: NIH 15614
SOURCE: JOURNAL OF IMMUNOLOGY, **(1997 Jun 1)** 158 (11) 5435-41.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970619

AB In addition to its role in coagulation, thrombin is involved in the inflammatory process by inducing vessel neutrophilic infiltration. Thrombin induces endothelial P-selectin expression and platelet activating factor release, which participate to induce early neutrophil adhesion and activation. We employed HUVEC and now show that thrombin induces the production of the chemokine IL-8 in a time- and dose-dependent fashion. Similarly, thrombin induced E-selectin expression on HUVEC. Both IL-8 secretion and E-selectin expression were preceded by an increase in steady state levels of the respective mRNAs. Thrombin action on HUVEC was inhibited by the specific thrombin inhibitor, hirudin. In addition, these effects of thrombin on HUVEC were mimicked by the 14-amino acid **thrombin receptor** agonist peptide, which triggers the native **thrombin receptor** in a similar fashion to thrombin itself. Although IL-1 and TNF-alpha also induce IL-8 and E-selectin, the thrombin effects in these experiments were not mediated by those cytokines, since neither IL-1 receptor antagonist nor anti-TNF-alpha Ab inhibited the effects of thrombin. Furthermore, IL-1alpha, IL-1beta, and TNF-alpha were not detected in the supernatants of thrombin-activated HUVEC. Although intracellular IL-1alpha was found in thrombin-activated HUVEC, **antisense** IL-1alpha had no inhibitory effect on IL-8 secretion. These results demonstrate that in addition to short term endothelial activation, thrombin also functions as a long acting proinflammatory agent by inducing endothelial synthesis of the mediators required for neutrophils activation and extravazation during inflammation.

L7 ANSWER 8 OF 83 MEDLINE
ACCESSION NUMBER: 97259279 MEDLINE
DOCUMENT NUMBER: 97259279 PubMed ID: 9105399
TITLE: Nonproteolytic activation of the **thrombin receptor** promotes human umbilical vein endothelial cell growth but not intracellular CA2+, prostacyclin, or permeability.
COMMENT: Erratum in: Biochem Pharmacol 1997 Jun 15;53(12):1945
AUTHOR: Schaeffer P; Riera E; Dupuy E; Herbert J M
CORPORATE SOURCE: Haemobiology Research Department, Sanofi Recherche, Toulouse, France.
SOURCE: BIOCHEMICAL PHARMACOLOGY, **(1997 Feb 21)** 53 (4) 487-91.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970507
Last Updated on STN: 19980206
Entered Medline: 19970501

AB Both thrombin and the synthetic tetracapeptide **thrombin receptor**-activating peptide (TRAP), recently described as a peptide mimicking the new amino terminus created by cleavage of the **thrombin receptor**, stimulated the proliferation of human umbilical vein endothelial cells (HUVEC) in culture. Although to a lesser extent, F-14, a tetradecapeptide representing the residues 365-378 of human prothrombin, also promoted HUVEC growth, thereby demonstrating that thrombin can stimulate HUVEC growth via both a proteolytic and a nonenzymatic pathway. Thrombin-TRAP, and F-14-induced HUVEC growth were inhibited by a **thrombin receptor** oligodeoxynucleotide **antisense**, showing that the growth-inducing effects of all 3 compounds were mediated through the same **thrombin receptor**. Thrombin and TRAP also stimulated intracellular Ca2+ increase, monolayer permeability increase, and prostacyclin release in HUVEC. None of these effects was observed with F-14 suggesting that thrombin-induced intracellular Ca2+ release, permeability increase, and prostacyclin release in HUVEC required catalytic cleavage of the receptor, whereas thrombin-induced growth might also be due to activation of the **thrombin receptor** through a nonproteolytic pathway.

L7 ANSWER 9 OF 83 MEDLINE
ACCESSION NUMBER: 97162152 MEDLINE
DOCUMENT NUMBER: 97162152 PubMed ID: 9009139
TITLE: Intimal hyperplasia following vascular injury is not inhibited by an **antisense thrombin receptor** oligodeoxynucleotide.
AUTHOR: Herbert J M; Guy A F; Lamarche I; Mares A M; Savi P; Dol F
CORPORATE SOURCE: Haemobiology Research Department, Sanofi Recherche, Toulouse, France.
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, **(1997 Feb)** 170 (2) 106-14.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 19970306
Entered Medline: 19970224

AB Thrombin is a multifunctional serine protease with central functions in hemostasis, but demonstration of its role in the initiation and maintenance of cell proliferation which occurs following vascular injury is still lacking. To determine the role played by thrombin and its receptor in neointimal accumulation of smooth muscle cells in a rabbit carotid artery model, we have used an 18 mer **antisense** phosphorothioate oligonucleotide (ODN) directed against the translation initiation region of the human **thrombin receptor** gene. The **antisense** ODN inhibited in a dose-dependent manner thrombin- or **thrombin receptor** activating peptide-induced human aortic smooth muscle cell proliferation. The growth-inhibitory effect of **thrombin receptor antisense** ODN was preventable by an excess of sense oligomer and specific for thrombin. The suppression of growth was accompanied by a marked decrease of the level of **thrombin receptor** expression as evidenced by [125I]-thrombin binding to smooth muscle cells. Under the same experimental conditions, the corresponding sense ODN was inactive. The effect of the **antisense** ODN on intimal smooth muscle hyperplasia

in rabbit carotid arteries subjected to endothelial injury was then investigated. The topical application of the **antisense** (500 microg/artery) but not the sense ODN dissolved in F127 pluronic gel around the injured artery resulted, 2 weeks after the application, in a dramatic reduction of the expression of the **thrombin receptor** mRNA and protein levels as determined by in situ hybridization and immunohistochemistry. However, intimal smooth muscle cell accumulation as estimated by an intimal to medial cross-sectional area ratio was reduced only by 2.7% (vs. 10.3% for the sense ODN), whereas r-hirudin (200 microg/kg/day, s.c.), a potent direct thrombin inhibitor significantly reduced the formation of neointima in denuded carotid arteries (35.4% inhibition, P = 0.03).

L7 ANSWER 10 OF 83 MEDLINE
ACCESSION NUMBER: 96310865 MEDLINE
DOCUMENT NUMBER: 96310865 PubMed ID: 8684486
TITLE: A non-muscle myosin required for embryonic polarity in Caenorhabditis elegans.
AUTHOR: Guo S; Kemphues K J
CORPORATE SOURCE: Section of Genetics and Development, Cornell University, Ithaca, New York 14853, USA.
SOURCE: NATURE, **(1996 Aug 1)** 382 (6590) 455-8.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U49263
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960828
Last Updated on STN: 19960828
Entered Medline: 19960819

AB Daughter cells with distinct fates can arise through intrinsically asymmetrical divisions. Before such divisions, factors crucial for determining cell fates become asymmetrically localized in the mother cell. In Caenorhabditis elegans, PAR proteins are required for the early asymmetrical divisions that establish embryonic polarity, and are asymmetrically localized in early blastomeres, although the mechanism of their distribution is not known. Here we report the identification in C. elegans of nonmuscle myosin II heavy chain (designated NMY-2) by means of its interaction with the **PAR-1** protein, a putative Ser/Thr protein kinase. Furthermore, injections of nmy-2 **antisense** RNA into ovaries of adult worms cause embryonic partitioning defects and lead to mislocalization of PAR proteins. We therefore conclude the NMY-2 is required for establishing cellular polarity in C. elegans embryos.

L7 ANSWER 11 OF 83 MEDLINE
ACCESSION NUMBER: 96181571 MEDLINE
DOCUMENT NUMBER: 96181571 PubMed ID: 8601636
TITLE: The proteinase activated receptor-2 (PAR-2) mediates mitogenic responses in human vascular endothelial cells.
AUTHOR: Mirza H; Yatsula V; Bahou W F
CORPORATE SOURCE: Department of Medicine, State University of New York at Stony Brook, 11794-8151, USA.
CONTRACT NUMBER: R01HL02431 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, **(1996 Apr 1)** 97 (7) 1705-14.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960517

Last Updated on STN: 19960517
Entered Medline: 19960507

AB Proteolytically cleaved receptors, typified by the functional **thrombin receptor** (TR), represent a novel class of receptors that mediate signaling events by functional coupling to G proteins. Northern blot analysis completed with a human proteinase activated receptor-2 (PAR-2) cDNA as probe demonstrated the approximately 3.5kb PAR-2 transcript in total cellular RNA from human umbilical vein endothelial cells (HUVEC). Microspectrofluorimetry using Fura2-loaded HUVEC demonstrated a dose-dependent elevation in intracellular calcium transients ([Ca2+]i) to murine PAR39-44 (SLIGRL, putative neoligand after cleavage), with an approximate EC50 of 30 microM, and evidence for homologous desensitization with complete recovery at 45 min. Xenopus oocytes microinjected with TR cRNA failed to respond to 200 microM PAR39-44, and TR-targeted **antisense** oligonucleotides specifically abrogated thrombin-induced but not PAR39-44-mediated [Ca2+]i, excluding the possibility that TR/PAR-2 cell-surface coexpression was structurally linked. HUVEC incubated with PAR39-44 demonstrated a dose- and time-dependent mitogenic response similar to that seen with thrombin or TR42-47 (TR-activating peptide, SFLLRN). Preactivation of HUVEC with either PAR39-44 or thrombin resulted in heterologous desensitization to the corresponding agonist, an effect that was mediated primarily by TR internalization as evaluated by immunofluorescence and quantitative ELISA. These results ascribe a previously unrecognized function to the PAR-2 receptor, imply that a natural enzyme agonist may circulate in plasma, and suggest the presence of an additional regulatory mechanism controlling receptor activation events in vascular endothelial cells.

L7 ANSWER 12 OF 83 MEDLINE
ACCESSION NUMBER: 96025755 MEDLINE
DOCUMENT NUMBER: 96025755 PubMed ID: 7592574
TITLE: Selective inhibition of **thrombin receptor** -mediated Ca2+ entry by protein kinase C beta.
AUTHOR: Xu Y; Ware J A
CORPORATE SOURCE: Cardiovascular Division, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts 02215, USA.
CONTRACT NUMBER: HL02271 (NHLBI)
HL38820 (NHLBI)
HL47032 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1995 Oct 13)** 270 (41) 23887-90.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951204

AB Thrombin initiates many physiological processes in platelets and other megakaryocyte-lineage cells by interacting with surface receptors and generating rises in cytoplasmic Ca2+; these rises result from both Ca2+ release from intracellular stores and receptor-mediated Ca2+ entry. Regulators that limit Ca2+ entry after its initiation by thrombin have not been identified. In this study, prevention of expression of a single protein kinase C isoenzyme (PKC beta) by **antisense** cDNA overexpressed in HEL cells, a human megakaryoblastic cell line that expresses thrombin receptors, promotes **thrombin receptor** -mediated Ca2+ entry without altering thrombin-induced intracellular release of Ca2+. The cytoplasmic Ca2+ rise initiated by endoperoxide analogs was not affected by inhibiting PKC beta. Overexpression of a cDNA encoding wild-type PKC beta mutated to prevent recognition by the **antisense** cDNA abolished the enhancement of Ca2+ influx following

thrombin. Thus, PKC beta appears to be a specific negative regulator of **thrombin receptor**-mediated Ca2+ entry.

L7 ANSWER 13 OF 83 MEDLINE
ACCESSION NUMBER: 95302638 MEDLINE
DOCUMENT NUMBER: 95302638 PubMed ID: 7783334
TITLE: Study of signal transduction through **thrombin receptor** and anti-thrombotic strategy using its controls.
AUTHOR: Kitajima I
CORPORATE SOURCE: Department of Laboratory Medicine, Kagoshima University.
SOURCE: RINSHO KETSUEKI. JAPANESE JOURNAL OF CLINICAL HEMATOLOGY, **(1995 Apr)** 36 (4) 303-7.
Journal code: 2984782R. ISSN: 0485-1439.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950726
Last Updated on STN: 19970203
Entered Medline: 19950714

AB Thrombin, a key enzyme in the hemostatic pathway, also has various effects on the function of human platelet, endothelial cells (HUVEC) and vascular smooth muscle cells (VSMC). A **thrombin receptor** (TR) has been cloned and is thought to mediate a variety of thrombin-induced responses. The post-receptor signals are mediated by several protein kinases responsible for NF-kappa B activation, and most thrombin-inducible genes have the kappa B sequence in the regulatory elements. TR stimulation resulted in a biphasic activation of NF-kappa B and the late phase of which required new NF-kappa B synthesis. We showed that the **antisense** oligodeoxynucleotides (ODNs) of NF-kappa B have a marked inhibitory effect on thrombin-induced cellular responses. Furthermore, E5510, a compound with anti-platelet activity preferentially inhibited the thrombin-inducible NF-kappa B activation. Therapeutic potential of inhibition of TR-NF-kappa B activation signaling for treatment with thrombotic disease is also indicated.

L7 ANSWER 14 OF 83 MEDLINE
ACCESSION NUMBER: 95221403 MEDLINE
DOCUMENT NUMBER: 95221403 PubMed ID: 7706289
TITLE: Growth-related responses in arterial smooth muscle cells are arrested by **thrombin receptor antisense** sequences.
AUTHOR: Chaikof E L; Caban R; Yan C N; Rao G N; Runge M S
CORPORATE SOURCE: Department of Surgery (Vascular Division), Emory University School of Medicine, Atlanta, Georgia 30322, USA.
CONTRACT NUMBER: HL-02414 (NHLBI)
HL-48667 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1995 Mar 31)** 270 (13) 7431-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19950518
Entered Medline: 19950510

AB The capacity of **antisense** sequences to the **thrombin receptor** to selectively inhibit **thrombin receptor** expression and limit mitogenic responses in vascular wall cells was investigated in vitro. Eight phosphorothioate

oligodeoxynucleotides based on the sequences of the rat **thrombin receptor** (including sense, **antisense**, scrambled, and missense controls) were synthesized, characterized, and purified by high performance liquid chromatography. The **antisense** oligodeoxynucleotide (ODN 4) inhibitory effect was sequence-specific and both time-and concentration-dependent. A reduction in serum or alpha-thrombin-induced smooth muscle cell (SMC) proliferation was noted as early as 3 days at 30 microM (82%; 6.17 +/- 1.01 versus 34.08 +/- 3.89 x 10(4) cells/well; $p < 0.05$) and at a dose as low as 15 microM after 4 days in culture (19%; $p < 0.05$). Nonspecific effects were enhanced after prolonged exposure of SMC to the **antisense** oligodeoxynucleotide (> or = 6 days). A reduction of inositol phosphate generation greater than 50% ($p < 0.05$) was detected after exposure of SMC to **antisense** but not to sense or scrambled nucleotide sequences. This was observed after stimulation with both thrombin and SFFLRN (**thrombin receptor** peptide agonist). Northern blot analysis and enzyme-linked immunosorbent assays revealed 50 and 22% decreases, respectively, in **thrombin receptor** mRNA and protein (cell surface) levels in **antisense** oligonucleotide-treated (72 h) SMC as compared to untreated cells, suggesting that **thrombin receptor** down-regulation occurred at the pretranslational level. Thus, **thrombin receptor**-specific **antisense** sequences inhibit growth-related effects both of serum and thrombin on smooth muscle cells, potentially providing a new strategy for selective inhibition of receptor-mediated arterial injury responses.

L7 ANSWER 15 OF 83 MEDLINE
ACCESSION NUMBER: 95168175 MEDLINE
DOCUMENT NUMBER: 95168175 PubMed ID: 7863981
TITLE: Role of the **thrombin receptor** in restenosis and atherosclerosis.
COMMENT: Comment in: Am J Cardiol. 1995 Feb 23;75(6):63B-64B
AUTHOR: Baykal D; Schmedtje J F Jr; Runge M S
CORPORATE SOURCE: Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.
CONTRACT NUMBER: HL-02414 (NHLBI)
HL-48557 (NHLBI)
SOURCE: AMERICAN JOURNAL OF CARDIOLOGY, **(1995 Feb 23)** 75 (6) 82B-87B. Ref: 36
Journal code: 0207277. ISSN: 0002-9149.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950404
Last Updated on STN: 19950404
Entered Medline: 19950323

AB Thrombus generation is central to thrombosis at vascular lesion sites, including post-PCTA acute reocclusion and chronic restenosis. Thrombin stimulates platelet activation, monocyte and neutrophil chemotaxis, and endothelial production of prothrombotic factors. The varied physiologic effects of thrombin are due to the widespread presence of thrombin receptors in many cell types. The receptor is uniquely activated: thrombin binds to the receptor at the thrombin anion-binding exosite, the receptor ligand ("tethered ligand") apparently being a sequence of 6 amino acids (SFLLRN). Thus, peptides corresponding to the sequence of the tethered ligand can stimulate almost all functions of native thrombin itself. Several intracellular signaling pathways have been identified as important in the restenosis process: the G protein-related pathway, cyclic adenosine monophosphate (cAMP) mediator pathway, and tyrosine kinase activation pathway. In situ hybridization has demonstrated an increase in

thrombin receptor mRNA throughout the period of neointimal and vascular lesion development. The mechanism of this increase is unknown, but may be mediated by multiple inflammatory modulators. Several strategies have been tested in animal models for inhibiting thrombin: (1) Hirudin not only prevents thrombin from cleaving fibrinogen, but also prevents **thrombin receptor** activation. (2) **Thrombin receptor** antagonist peptides block platelet aggregation effects of thrombin. (3) Mono- and polyclonal antibodies inhibit **thrombin receptor** activation. (4) **Antisense** oligonucleotides block **thrombin receptor** expression.

L7 ANSWER 16 OF 83 MEDLINE
ACCESSION NUMBER: 95124328 MEDLINE
DOCUMENT NUMBER: 95124328 PubMed ID: 7823939
TITLE: Expression cloning of oncogenes by retroviral transfer of cDNA libraries.
AUTHOR: Whitehead I; Kirk H; Kay R
CORPORATE SOURCE: Department of Medical Genetics, University of British Columbia, Canada.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, **(1995 Feb)** 15 (2) 704-10.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950223
Last Updated on STN: 19980206
Entered Medline: 19950216

AB a cDNA library transfer system based on retroviral vectors has been developed for expression cloning in mammalian cells. The use of retroviral vectors results in stable cDNA transfer efficiencies which are at least 100-fold higher than those achieved by transfection and therefore enables the transfer and functional screening of very large libraries. In our initial application of retroviral transfer of cDNA libraries, we have selected for cDNAs which induce oncogenic transformation of NIH 3T3 fibroblasts, as measured by loss of contact inhibition of proliferation. Nineteen different transforming cDNAs were isolated from a total of 300,000 transferred cDNA clones. Three of these cDNAs were derived from known oncogenes (raf-1, lck, and ect2), while nine others were derived from genes which had been cloned previously but were not known to have the ability to transform fibroblasts (beta-catenin, **thrombin receptor**, phospholipase C-gamma 2 and Spi-2 protease inhibitor genes). The Spi-2 cDNA was expressed in **antisense** orientation and therefore is likely to act as an inhibitor of an endogenous transformation suppressor. Seven novel cDNAs with transforming activities, including those for three new members of the CDC24 family of guanine nucleotide exchange factors, were also cloned from the retroviral cDNA libraries. Retroviral transfer of libraries should be generally useful for cloning cDNAs which confer selectable phenotypes on many different types of mammalian cells.

L7 ANSWER 17 OF 83 MEDLINE
ACCESSION NUMBER: 95071419 MEDLINE
DOCUMENT NUMBER: 95071419 PubMed ID: 7980566
TITLE: Involvement of NF-kappa B activation in thrombin-induced human vascular smooth muscle cell proliferation.
AUTHOR: Nakajima T; Kitajima I; Shin H; Takasaki I; Shigeta K; Abeyama K; Yamashita Y; Tokioka T; Soejima Y; Maruyama I
CORPORATE SOURCE: Department of Laboratory Medicine, Faculty of Medicine, University of Kagoshima, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,

(1994 Oct 28) 204 (2) 950-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941130

AB A **thrombin receptor** has been cloned and is thought to mediate a variety of thrombin-induced responses. However, the transcription factors important for postreceptor signaling have been little clarified.. The post-receptor signals are mediated by several protein kinases responsible for NF-kappa B activation, and most thrombin-inducible genes have the kappa B sequence in the regulatory elements. The possibility that NF-kappa B may participate in thrombin signaling was therefore investigated in cultured human vascular smooth muscle cells (VSMCs). **Thrombin receptor** stimulation resulted in activation of NF-kappa B. Furthermore, treatment of cells with **antisense** p65 ODNs of NF-kappa B inhibited thrombin-stimulated growth of VSMC in vitro. Results indicate that the activation of NF-kappa B is involved in thrombin signaling and that this pathway causes the proliferation of VSMC induced by thrombin. Therapeutic potential of **antisense** NF-kappa B ODNs for the treatment with atherosclerosis and restenosis is also indicated.

L7 ANSWER 18 OF 83 MEDLINE
ACCESSION NUMBER: 94380027 MEDLINE
DOCUMENT NUMBER: 94380027 PubMed ID: 8093037
TITLE: E5510 antagonizes **thrombin receptor** signals by inhibiting NF-kappa B activation.
AUTHOR: Nakajima T; Kitajima I; Shin H; Matsumoto W; Soejima Y; Maruyama I
CORPORATE SOURCE: Department of Laboratory Medicine, Faculty of Medicine, University of Kagoshima, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1994 Sep 15)** 203 (2) 1181-7.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941031
Last Updated on STN: 19970203
Entered Medline: 19941018

AB We have recently demonstrated that NF-kappa B is involved in a thrombin-signaling and that the **antisense** oligodeoxynucleotides (ODNs) of NF-kappa B has a marked inhibitory effect on thrombin-induced cellular responses. In this study, we demonstrate that E5510 (4-cyano-5,5-bis(methoxyphenyl)-4-pentenoic acid), a compound with anti-platelet activity preferentially inhibits the thrombin-inducible NF-kappa B activation and then antagonizes the following thrombin-induced cellular responses, proliferation and cytokines production in vascular smooth muscle cell, and the adherency of differentiated HL-60 cells. These data suggest that E5510 is an anti-atherosclerotic or anti-restenotic drug induced by thrombin.

L7 ANSWER 19 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:461098 CAPLUS
DOCUMENT NUMBER: 131:208829
TITLE: Effect of **antisense thrombin receptor** gene on the proliferation of human

vascular smooth muscle cells

AUTHOR(S): Zhang, Qian; Meng, Xianmin; Jiang, Yuxin; Ding, Jinfeng; Tang, Jian; Chen, Guanghui

CORPORATE SOURCE: Gardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100037, Peop. Rep. China

SOURCE: Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao (**1999**), 15(3), 484-487
CODEN: ZSHXF2; ISSN: 1007-7626

PUBLISHER: Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao Bianweihui

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB Restenosis after angioplasty severely limits the final effect of this therapeutic technique. To study the fundamental mechanisms of restenosis and search for an effectively preventive approach, an eukaryotic expression vector (pcDNA3/ATR) contg. a partial **antisense thrombin receptor** (ATR) gene was constructed by **antisense** RNA technique. The inhibition of the recombinant vector proliferation of cultured human aortic smooth muscle cells (ASMC) was studied after introducing pcDNA3/ATR into ASMC instantaneously. The results showed that 3H-TdR incorporation in the transfected human ASMC was inhibited with pcDNA3/ATR in a dose-dependent manner. The expression of a partial **antisense thrombin receptor** gene could inhibit the proliferation of human ASMC.

L7 ANSWER 20 OF 83 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:421621 CAPLUS

DOCUMENT NUMBER: 129:159449

TITLE: Study of signal transduction through **thrombin receptor** in vascular smooth muscle cell

AUTHOR(S): Kitajima, Isao; Maruyama, Ikuo

CORPORATE SOURCE: Dep. Mol. Lab. Med., Kagoshima Univ., Kagoshima, Japan

SOURCE: Domyaku Koka (**1998**), 25(6/7), 225-229
CODEN: DOMKDM; ISSN: 0386-2682

PUBLISHER: Nippon Domyaku Koka Gakkai

DOCUMENT TYPE: Journal; General Review

LANGUAGE: Japanese

AB A review with 14 refs. Thrombin acts on the vascular endothelium to stimulate prodn. of plasminogen activator inhibitor and the potent smooth muscle cell mitogen platelet-derived growth factor, following proliferation of smooth muscle cell. A **thrombin receptor** has been cloned and is though to mediate a variety of thrombin-induced responses. The high expression of **thrombin receptor** in atherosclerotic lesions indicates a possible role **thrombin receptor** activation in restenosis and in atherogenesis itself. Cleavage of extracellular amino-terminus at this site is necessary and sufficient for receptor activation. The new amino terminus than function as a tethered ligand and stimulates receptor, which is essentially a peptide receptor predominantly by intramol. ligand, called as **thrombin receptor** activating peptide (TRAP). The post-receptor signals are studied. We obsd. increase of calcium influx and activation of protein kinase C (PKC) in cultured vascular smooth muscle cells stimulated by thrombin or TRAP. Next, the **thrombin receptor** signals are mediated by several protein kinases responsible for nuclear factor kappa B (NF-.kappa.B), and most thrombin-inducible genes have the .kappa.B sequence in the regulatory elements. Thrombin stimulation resulted in a biphasic activation of NF-.kappa.B, the early phase of which indicated nuclear translocation of NF-.kappa.B and the late phase of which required new synthesis. We showed that the **antisense** oligodeoxynucleotides of NF-.kappa.B have a marked inhibitory effect on thrombin-induced cellular responses. Furthermore, E5510, a compd. with anti-platelet activity preferentially inhibited the thrombin-inducible NF-.kappa.B activation. Thrombin

inhibitors including thrombomodulin have been tried to prevent thrombin-mediated arteriosclerosis. Furthermore, therapeutic potential of inhibition of **thrombin receptor**-NF-.kappa.B activation signaling for treatment such as **antisense** strategy is also indicated. Roles of thrombin and thrombin receptors in pathogenesis of atherosclerosis are also discussed.

L7 ANSWER 21 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:119221 CAPLUS
DOCUMENT NUMBER: 126:127885
TITLE: Cloning and cDNA sequence of human liver **thrombin receptor** homolog and its diagnostic and therapeutic uses
INVENTOR(S): Coleman, Roger; Au-young, Janice; Bandman, Olga; Seilhamer, Jeffrey J.
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640040	A2	19961219	WO 1996-US8948	19960604 <--
WO 9640040	A3	19970109		
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 5686597	A	19971111	US 1995-467125	19950606 <--
CA 2223077	AA	19961219	CA 1996-2223077	19960604 <--
AU 9659858	A1	19961230	AU 1996-59858	19960604 <--
AU 721194	B2	20000629		
EP 832128	A2	19980401	EP 1996-917198	19960604 <--
R: BE, DE, ES, FR, GB, IT, NL				
JP 11507519	T2	19990706	JP 1996-501392	19960604 <--
US 5869633	A	19990209	US 1997-911320	19970814 <--
US 6143870	A	20001107	US 1998-217101	19981221
US 2002128443	A1	20020912	US 2001-997522	20011128

PRIORITY APPLN. INFO.:

US 1995-467125	A	19950606
WO 1996-US8948	W	19960604
US 1997-911320	A3	19970814
US 1998-217101	A3	19981221
US 2000-643383	A1	20000821

AB The nucleotide and deduced amino acid sequences are provided for a novel **thrombin receptor** homolog (TRH), whose cDNA was identified and cloned from a human liver cDNA library. TRH is a 7-transmembrane receptor and is most similar to the human **thrombin receptor** identified by P. M. Dennington and M. C. Berndt (1994), as well as to residues 94-155 of the platelet activating factor receptor. The present invention also provides for **antisense** mols. to the nucleotide sequences which encode TRH, diagnostic tests based on TRH encoding nucleic acid mols., expression vectors for the prodn. of purified TRH, antibodies capable of binding to TRH, hybridization probes or oligonucleotides for the detection of TRH-encoding nucleotide sequences, genetically engineered host cells for the expression of TRH, and antagonists, antibodies and inhibitors which bind to the polypeptide TRH.

L7 ANSWER 22 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:299219 CAPLUS

DOCUMENT NUMBER: 125:6180
TITLE: Amyloid .beta.-peptide alters thrombin-induced calcium responses in cultured human neural cells
AUTHOR(S): Mattson, Mark P.; Begley, James G.
CORPORATE SOURCE: Sanders-Brown Research Center Aging, University Kentucky, Lexington, KY, 40536, USA
SOURCE: Amyloid (**1996**), 3(1), 28-40
CODEN: AIJIET; ISSN: 1350-6129
PUBLISHER: Parthenon Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The presence of prothrombin, thrombin receptors and thrombin inhibitors in the brain, together with recent evidence that thrombin can affect neuronal outgrowth and survival, suggests that thrombin signaling may be involved in neuronal plasticity and injury. In Alzheimer's disease (AD), thrombin is assocd. with plaques comprised largely of amyloid .beta.-peptide (A.beta.). Because recent studies have shown that A.beta. can destabilize neuronal calcium homeostasis, and because thrombin receptors are linked to inositol phospholipid hydrolysis and elevation of [Ca2+]i, we tested the hypothesis that A.beta. modifies [Ca2+]i responses to thrombin. Studies using **thrombin receptor** antibodies and **antisense** oligodeoxynucleotide technol. to suppress expression of thrombin receptors demonstrated that human SH-SY5Y neuroblastoma cells expressed thrombin receptors linked to Ca2+ release from intracellular stores. Relatively short term pretreatment (1 to 3 h) of the SH-SY5Y cells with A.beta.25-35 or A.beta.1-40 resulted in a significant two- to three-fold enhancement of thrombin-induced elevation of [Ca2+]i. In contrast, chronic pretreatment with A.beta.s (8 to 16 h) resulted in an attenuation or complete abrogation of [Ca2+]i responses to thrombin. Imaging of thiobarbituric acid fluorescence demonstrated that A.beta. induced lipid peroxidn., and the effects of both short and long term exposure to A.beta. on [Ca2+]i responses, were largely abrogated in cultures pretreated with antioxidants. Thus, A.beta. induces lipid peroxidn. which impairs **thrombin receptor**-mediated Ca2+ signaling. The data suggest that thrombin plays roles in neuronal plasticity and neurodegenerative processes, and A.beta. may induce aberrant thrombin signal transduction which could contribute to the pathogenesis of AD.

L7 ANSWER 23 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:42911 CAPLUS
DOCUMENT NUMBER: 124:83225
TITLE: Transgenic baby hamster kidney (BHK) cells induced for high expression of human **thrombin receptor** cDNA and use of **antisense** DNA for inhibiting **thrombin receptor**
INVENTOR(S): Takada, Masahiro; Ito, Osamu; Ogushi, Motoharu; Kobayashi, Hiroko; Yamada, Toshe; Tanaka, Hiroshi
PATENT ASSIGNEE(S): Eisai Co Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07289268	A2	19951107	JP 1994-109146	19940426 <--

AB BHK cells transformed with plasmid pK4K/hTR encoding human **thrombin receptor** are treated with basic fibroblast growth factor (bFGF) to induce high expression of the receptor. The system is useful in screening **antisense** DNA that are inhibitory to the receptors, which **antisense** DNA can be used for the prepn.

of therapeutics or prophylactics for the diseases assocd. with the receptors. Inhibition of the bFGF-induced expression of human **thrombin receptor** by an **antisense** DNA was demonstrated.

L7 ANSWER 24 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:475667 CAPLUS
DOCUMENT NUMBER: 122:236436
TITLE: Role of the **thrombin receptor** in restenosis and atherosclerosis
AUTHOR(S): Baykal, Demir; Schmedtje, John F. Jr.; Runge, Marschall S.
CORPORATE SOURCE: School of Medicine, Emory University, Atlanta, GA, USA
SOURCE: American Journal of Cardiology (**1995**), 75(6), 82B-87B
CODEN: AJCDAG; ISSN: 0002-9149
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 36 refs. Thrombus generation is central to thrombosis at vascular lesion sites, including post-PCTA acute reocclusion and chronic restenosis. Thrombin stimulates platelet activation, monocyte and neutrophil chemotaxis, and endothelial prodn. of prothrombotic factors. The varied physiol. effects of thrombin are due to the widespread presence of thrombin receptors in many cell types. The receptor is uniquely activated: thrombin binds to the receptor at the thrombin anion-binding exosite, the receptor ligand ("tethered ligand") apparently being a sequence of 6 amino acids (SFLLRN). Thus, peptides corresponding to the sequence of the tethered ligand can stimulate almost all functions of native thrombin itself. Several intracellular signaling pathways have been identified as important in the restenosis process: the G protein-related pathway, cyclic adenosine monophosphate (cAMP) mediator pathway, and tyrosine kinase activation pathway. In situ hybridization has demonstrated an increase in **thrombin receptor** mRNA throughout the period of neointimal and vascular lesion development. The mechanism of this increase is unknown, but may be mediated by multiple inflammatory modulators. Several strategies have been tested in animal models for inhibiting thrombin: Hirudin not only prevents thrombin from cleaving fibrinogen, but also prevents **thrombin receptor** activation. **Thrombin receptor** antagonist peptides block platelet aggregation effects of thrombin. Mono- and polyclonal antibodies inhibit **thrombin receptor** activation. **Antisense** oligonucleotides block **thrombin receptor** expression.

L7 ANSWER 25 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:423305 CAPLUS
DOCUMENT NUMBER: 115:23305
TITLE: Identification and analysis of **antisense** RNA target regions of the human immunodeficiency virus type 1
AUTHOR(S): Rittner, Karola; Sczakiel, Georg
CORPORATE SOURCE: Inst. Virusforsch., Dtsch. Krebsforschungszent., Heidelberg, D-6900, Germany
SOURCE: Nucleic Acids Research (**1991**), 19(7), 1421-6
CODEN: NARHAD; ISSN: 0305-1048
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Antisense** RNA, transcribed intracellularly from constitutive expression cassettes, inhibits the replication of the human immunodeficiency virus type 1 (HIV-1) as demonstrated by a quant. microinjection assay in human SW480 cells. Infectious proviral HIV-1 DNA was co-microinjected with a 5-fold molar excess of plasmids expressing **antisense** RNA complementary to a set of ten different HIV-1 target regions. The most inhibitory **antisense** RNA expression plasmids

were targeted against a 1 kb region within the gag open reading frame and against a 562 base region contg. the coding sequences for the regulatory viral proteins tat and rev. Exptl. evidence is presented that the **antisense** principle is the inhibitory mechanism in this assay system.

L7 ANSWER 26 OF 83 LIFESCI COPYRIGHT 2002 CSA
ACCESSION NUMBER: 2000:24543 LIFESCI
TITLE: **Thrombin receptor** homolog polynucleotide
AUTHOR: Coleman, R.; Au-Young, J.; Bandman, O.; Seilhamer, J.
CORPORATE SOURCE: Incyte Pharmaceuticals, Inc.
SOURCE: (**19990209**) . US Patent: 5869633; US CLASS: 536/23.1; 536/24.5; 536/23.5; 530/350..
DOCUMENT TYPE: Patent
FILE SEGMENT: W3
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The present invention provides nucleotide and amino acid sequences that identify and encode a novel **thrombin receptor** homolog (TRH) expressed in human liver. The present invention also provides for **antisense** molecules to the nucleotide sequences which encode TRH, diagnostic tests based on TRH encoding nucleic acid molecules, expression vectors for the production of purified TRH, antibodies capable of binding specifically to TRH, hybridization probes or oligonucleotides for the detection of TRH-encoding nucleotide sequences, genetically engineered host cells for the expression of TRH, and antagonists, antibodies and inhibitors with specific binding activity for the polypeptide TRH.

L7 ANSWER 27 OF 83 USPATFULL
ACCESSION NUMBER: 2002:303872 USPATFULL
TITLE: Lipid kinase
INVENTOR(S): Vanhaesebroeck, Bart, London, UNITED KINGDOM
Waterfield, Michael Derek, London, UNITED KINGDOM
PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6482623	B1	20021119	
	WO 9746688		19971211	<--
APPLICATION INFO.:	US 1998-194640		19981201	(9)
	WO 1997-GB1471		19970530	
			19981201	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1996-11460	19960601

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Achutamurthy, Ponnathapu
ASSISTANT EXAMINER: Rao, Manjunath N.
LEGAL REPRESENTATIVE: Fulbright & Jaworski LLP
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 18 Drawing Page(s)
LINE COUNT: 1568
AB The invention relates to a novel lipid kinase which is part of the PI3 Kinase family. PI3 Kinases catalyze the addition of phosphate to inositol generating inositol mono, di and triphosphate. Inositol phosphates have been implicated in regulating intracellular signalling cascades resulting in alternations in gene expression which, amongst other effects, can result in cytoskeletal remodelling and modulation of cellular motility. More particularly the invention relates to a novel

human PI3 Kinase, p110.delta. which interacts with p85, has a broad phosphoinositide specificity and is sensitive to the same kinase inhibitors as PI3 Kinase p110.alpha.. However in contrast to previously identified PI3 Kinases which show a ubiquitous pattern of expression, p110.delta. is selectively expressed in leucocytes. Importantly, p110.delta. shows enchanced expression in most melanomas tested and therefore may play a crucial role in regulating the metastatic property exhibited by melanomas. The identification of agents that enhance or reduce p110.delta. activity may therefore prevent cancer metastasis.

L7 ANSWER 28 OF 83 USPATFULL

ACCESSION NUMBER: 2002:262057 USPATFULL
TITLE: Agents for the prevention of damages caused by stress conditions
INVENTOR(S): Bar-Shavit, Rachel, Jerusalem, ISRAEL
PATENT ASSIGNEE(S): Hadasit Medical Research Services & Development Limited, Jerusalem, ISRAEL (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6461611	B1	20021008	
	WO 9942483		19990826	<--
APPLICATION INFO.:	US 2000-600031		20000720	(9)
	WO 1999-IL95		19990216	
			20000720	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	IL 1998-123349	19980218

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Tate, Christopher R.
ASSISTANT EXAMINER: Winston, Randall
LEGAL REPRESENTATIVE: Oliff & Berridge, PLC
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 634
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Pharmaceutical compositions for the treatment of a decrease in the levels of protease activated receptor (PAR) mRNA caused by a lack or decrease of oxygen level and/or a lack or decrease of blood flow including pharmaceutically acceptable carriers and activators of PAR are provided. Methods for prevention of a decrease in the levels of protease-activated receptor PAR mRNA caused by lack or decrease in the oxygen level and/or lack or decrease in blood flow are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 29 OF 83 USPATFULL

ACCESSION NUMBER: 2002:70095 USPATFULL
TITLE: Methods and compositions for inhibiting inflammation and angiogenesis comprising a mammalian CD97 .alpha. subunit
INVENTOR(S): Kelly, Kathleen, North Potomac, MD, United States
PATENT ASSIGNEE(S): The United States of America as represented by the Secretary of the Department of Health and Human Services, Washington, DC, United States (U.S. government)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6365712	B1	20020402

APPLICATION INFO.:	WO 9817796	19980430	<--
	US 1999-284819	19990820 (9)	
	WO 1997-US19772	19971024	
		19990820 PCT 371 date	

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-27871P	19961025 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Huff, Sheela
ASSISTANT EXAMINER: Harris, Alana M.
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew LLP
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 3805
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated proteins comprising the T-cell surface antigen CD97 .alpha. are provided. Compositions and methods for making and detecting CD97 .alpha. are also provided. Further, the invention provides diagnostic and therapeutic methods and compositions for medical conditions involving CD97.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 30 OF 83 USPATFULL
ACCESSION NUMBER: 2001:196837 USPATFULL
TITLE: Human MEKK proteins, corresponding nucleic acid molecules, and uses therefor
INVENTOR(S): Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S): National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6312934	B1	20011106	
	WO 9947686		19990923	<--
APPLICATION INFO.:	US 2000-423890		20000306	(9)
	WO 1999-US5556		19990315	
			20000306	PCT 371 date
			20000306	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-78153P	19980316 (60)
	US 1998-99165P	19980904 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Monshipouri, M.
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP, Lauro, Esq, Peter C., Milasincic, Esq, Debra J.
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 35 Drawing Figure(s); 35 Drawing Page(s)
LINE COUNT: 2856
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated nucleic acid molecules encoding human MEKK proteins, and isolated MEKK proteins, are provided. The invention further provides **antisense** nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression vectors have been introduced and nonhuman transgenic animals carrying a human MEKK transgene. The invention

further provides human MEKK fusion proteins and anti-human MEKK antibodies. Methods of using the human MEKK proteins and nucleic acid molecules of the invention are also disclosed, including methods for detecting human MEKK activity in a biological sample, methods of modulating human MEKK activity in a cell, and methods for identifying agents that modulate the activity of human MEKK.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d history

     (FILE 'HOME' ENTERED AT 13:53:01 ON 04 DEC 2002)

     FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL, BIOSIS' ENTERED AT
     13:53:17 ON 04 DEC 2002
L1         82751 S THR OR F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN R
L2          8539 S L1 AND (ANTISENSE OR RIBOZYME OR TRIPLEX)
L3           587 S L1 (P) (ANTISENSE OR RIBOZYME OR TRIPLEX)
L4          7436 S F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN RECEPTOR
L5           272 S L4 AND (ANTISENSE OR RIBOZYME OR TRIPLEX)
L6           212 DUP REM L5 (60 DUPLICATES REMOVED)
L7            83 S L6 AND PY<2000

=> s l2 and (placenta or implantation)
L8         2888 L2 AND (PLACENTA OR IMPLANTATION)

=> s l2 and (placenta)
L9         1989 L2 AND (PLACENTA)

=> s l2 and (placenta and implantation)
L10         439 L2 AND (PLACENTA AND IMPLANTATION)

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          436 DUP REM L10 (3 DUPLICATES REMOVED)

=> s l11 and py<2000
   3 FILES SEARCHED...
   5 FILES SEARCHED...
L12          63 L11 AND PY<2000

=> d l12 ibib abs 1-30

L12  ANSWER 1 OF 63     MEDLINE
ACCESSION NUMBER:   1998364972     MEDLINE
DOCUMENT NUMBER:    98364972   PubMed ID: 9701242
TITLE:              Thrombin receptor overexpression in
                    malignant and physiological invasion processes.
AUTHOR:             Even-Ram S; Uziely B; Cohen P; Grisaru-Granovsky S; Maoz M;
                    Ginzburg Y; Reich R; Vlodavsky I; Bar-Shavit R
CORPORATE SOURCE:   Department of Oncology, Hadassah-Hebrew University
                    Hospital, Jerusalem, Israel.
SOURCE:             NATURE MEDICINE, (1998 Aug) 4 (8) 909-14.
                    Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199808
ENTRY DATE:         Entered STN: 19980903
                    Last Updated on STN: 19980903
                    Entered Medline: 19980825
AB   Although the involvement of soluble and matrix-immobilized proteases in
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tumor cell invasion and metastasis is well recognized, the role of proteolytically activated cell surface receptors has not been elucidated. We report here that **thrombin receptor**, a member of the protease-activated receptor family, is preferentially expressed in highly metastatic human breast carcinoma cell lines and breast carcinoma biopsy specimens. Introduction of **thrombin receptor antisense** cDNA considerably inhibited the invasion of metastatic breast carcinoma cells in culture through a reconstituted basement membrane. During placental **implantation** of the human embryo, **thrombin receptor** is transiently expressed in the invading cytotrophoblasts. These results emphasize the involvement of **thrombin receptor** in cell invasion associated with tumor progression and normal embryonic development.

L12 ANSWER 2 OF 63 USPATFULL
ACCESSION NUMBER: 2002:303979 USPATFULL
TITLE: Use of neomycin for treating angiogenesis-related diseases
INVENTOR(S): Hu, Guo-fu, Brookline, MA, United States
Vallee, Bert L., Boston, MA, United States
PATENT ASSIGNEE(S): Endowment for Research in Human Biology, Inc., Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6482802	B1	20021119	
	WO 9958126		19991118	<--
APPLICATION INFO.:	US 2000-700436		20001109	(9)
	WO 1999-US10269		19990511	
			20001109	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-84921P	19980511 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Raymond, Richard L.
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 63
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 2312
AB The present invention is directed to using neomycin or an analogue thereof as an therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compositions comprising (a) neomycin or an analogue and, optionally, (b) another anti-angiogenic agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogues having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases.

L12 ANSWER 3 OF 63 USPATFULL
ACCESSION NUMBER: 2002:160542 USPATFULL
TITLE: Method of screening for a modulator of angiogenesis
INVENTOR(S): Lau, Lester F., Chicago, IL, United States
PATENT ASSIGNEE(S): Munin Corporation, Chicago, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6413735	B1	20020702

	WO 9733995	19970918	<--
APPLICATION INFO.:	US 1999-142569	19990402 (9)	
	WO 1997-US4193	19970314	
		19990402 PCT 371 date	

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-13958P	19960315 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Crouch, Deborah
ASSISTANT EXAMINER: Woitach, Joseph T.
LEGAL REPRESENTATIVE: Katten Muchin Zavis
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 4088
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Polynucleotides encoding mammalian ECM signalling molecules affecting the cell adhesion, migration, and proliferation activities characterizing such complex biological processes as angiogenesis. chondrogenesis, and oncogenesis, are provided. The polynucleotide compositions include DNAs and RNAs comprising part, or all, of an ECM signalling molecule coding sequence, or biological equivalents. Polypeptide compositions are also provided. The polypeptide compositions comprise mammalian ECM signalling molecules, peptide fragments, inhibitory peptides capable of interacting with receptors for ECM signalling molecules, and antibody products recognizing Cyr61. Also provided are methods for producing mammalian ECM signalling molecules. Further provided are methods for using mammalian ECM signalling molecules to screen for, and/or modulate, disorders associated with angiogenesis, chondrogenesis, and oncogenesis; ex vivo methods for using mammalian ECM signalling molecules to prepare blood products are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 4 OF 63 USPATFULL
ACCESSION NUMBER: 2002:88222 USPATFULL
TITLE: Methods to diagnose a required regulation of trophoblast invasion
INVENTOR(S): Caniggia, Isabella, Toronto, CANADA
Post, Martin, 328 Wellesley Street East, Toronto, CANADA M4X 1H3
Lye, Stephen, Toronto, CANADA
PATENT ASSIGNEE(S): The Hospital for Sick Children (HSC), Toronto, CANADA (non-U.S. corporation)
Mount Sinai Hospital Corporation, Toronto, CANADA (non-U.S. corporation)
Post, Martin, Toronto, CANADA (non-U.S. individual)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6376199	B1	20020423	
	WO 9840747		19980917	<--
APPLICATION INFO.:	US 1999-380662		19991221	(9)
	WO 1998-CA180		19980305	
			19991221	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-39919P	19970307 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED

PRIMARY EXAMINER: Eyler, Yvonne
ASSISTANT EXAMINER: Andres, Janet L.
LEGAL REPRESENTATIVE: Merchant & Gould P.C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1,9
NUMBER OF DRAWINGS: 19 Drawing Figure(s); 21 Drawing Page(s)
LINE COUNT: 2297
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods are provided for the diagnosis and treatment of patients with increased risk of preeclampsia. The methods involve measuring levels of TGF-.beta..sub.3, receptors of cytokines of the TG.beta. family, or HIF-1.alpha..

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 5 OF 63 USPATFULL
ACCESSION NUMBER: 2002:63687 USPATFULL
TITLE: Prognostic compositions for prostate cancer and methods of use thereof
INVENTOR(S): Tricoli, James V., 106 Clover Leaf La., North Wales, PA, United States 19454
Rondinelli, Rachel, 418 Candlewood Way, Harleysville, PA, United States 19438

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6361948	B1	20020326	
	WO 9909215		19990225	<--
APPLICATION INFO.:	US 2000-485549		20001109	(9)
	WO 1998-US16768		19980813	
			20001109	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-55285P	19970813 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Horlick, Kenneth R.
LEGAL REPRESENTATIVE: Dean Dorfman Herrell & Skillman
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 1789
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a novel nucleic acid molecule, CLAR1, isolated from a human adult heart cDNA library. This cDNA is derived from a novel gene that represents a late stage-specific marker for prostate cancer progression. The CLAR1 cDNA, along with its encoded protein and antibodies thereto, provides a biological marker for aggressive prostate cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 6 OF 63 USPATFULL
ACCESSION NUMBER: 2001:102606 USPATFULL
TITLE: Synthetic mammalian .alpha.-n-acetylglucosaminidase and genetic sequences encoding same
INVENTOR(S): Hopwood, John Joseph, Stonyfell, Australia
Scott, Hamish Steele, Geneva, Switzerland
Weber, Birgit, Hackney, Australia
Blanch, Lianne, Grange, Australia
Anson, Donald Stewart, Thebarton, Australia
PATENT ASSIGNEE(S): Women's and Children's Hospital, Australia (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6255096	B1	20010703	
	WO 9719177		19970529	<--
APPLICATION INFO.:	US 1999-77354		19990422	(9)
	WO 1996-AU747		19961122	
			19990422	PCT 371 date
			19990422	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	AU 1995-6748	19951123

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Rao, Manjunath
LEGAL REPRESENTATIVE: Pokalsky, Ann R.
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1469
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates generally to mammalian .alpha.-N-acetyglucosaminidase and to genetic sequences encoding same and to their use in the investigation, diagnosis and treatment of subjects suspected of or suffering from .alpha.-N-acetylglucosaminidase deficiency.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 7 OF 63 USPATFULL

ACCESSION NUMBER: 2001:71683 USPATFULL
TITLE: Persephin and related growth factors
INVENTOR(S): Johnson, Jr., Eugene M., St. Louis, MO, United States
Milbrandt, Jeffrey D., St. Louis, MO, United States
Kotzbauer, Paul T., Swarthmore, PA, United States
Lampe, Patricia A., St. Louis, MO, United States
PATENT ASSIGNEE(S): Washington University, St. Louis, MO, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6232449	B1	20010515	
	WO 9733911		19970918	<--
APPLICATION INFO.:	US 1998-981739		19980831	(8)
	WO 1997-US3461		19970314	
			19980831	PCT 371 date
			19980831	PCT 102(e) date

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-615944, filed on 14 Mar 1996, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Chan, Christina Y.
ASSISTANT EXAMINER: Hayes, Robert C.
LEGAL REPRESENTATIVE: Howell & Haferkamp, L.C.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 28 Drawing Figure(s); 27 Drawing Page(s)
LINE COUNT: 3790
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A novel growth factor, persephin, which belongs to the GDNF/neurturin family of growth factors, is disclosed. The mouse and rat amino acid sequences have been identified. Mouse and rat persephin genomic DNA

sequences have been cloned and sequenced and the respective cDNA sequences identified. In addition, methods for treating degenerative conditions using persephin, methods for detecting persephin gene alterations and methods for detecting and monitoring patient levels of persephin are provided. Methods for identifying additional members of the persephin-neurturin-GDNF family of growth factors are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 8 OF 63 USPATFULL

ACCESSION NUMBER: 2001:60112 USPATFULL

TITLE: Transgenic non-human mammal expressing the DNA sequence encoding kappa casein mammary gland and milk

INVENTOR(S): Hansson, Lennart, Ume.ang., Sweden
Stromqvist, Mats, Ume.ang., Sweden
Bergstrom, Sven, Ume.ang., Sweden
Hernell, Olle, Ume.ang., Sweden
Tornell, Jan, Vastra, Sweden

PATENT ASSIGNEE(S): Symbicom Aktiebolag, Umea, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6222094	B1	20010424	
	WO 9315196		19930805	<--
APPLICATION INFO.:	US 1994-256799		19941206	(8)
	WO 1993-DK24		19930125	
			19941206	PCT 371 date
			19941206	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1992-88	19920123

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Crouch, Deborah
LEGAL REPRESENTATIVE: Cooper, Iver P.
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Figure(s); 18 Drawing Page(s)
LINE COUNT: 3140
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to an expression system comprising a DNA sequence encoding a polypeptide which ha a biological activity of human .kappa.-casein, the system comprising a 5'-flanking sequence capable of mediating expression of said DNA sequence. In preferred embodiments the 5'-flanking sequence is from a milk protein gene of a mammal such as a casein gene or whey acidic protein (WAP) gene and the DNA sequence contains at least one intron sequence. The invention further relates to DNA sequences, replicable expression vectors and cells harboring said vectors, recombinant polypeptide e.g. in glycosylated form, and milk, infant formula or nutrient supplement comprising recombinant polypeptide. The invention also relates to a method for producing a transgenic non-human mammal comprising injecting an expression system as defined above and optionally a further DNA encoding .beta.-casein or an analog, variant or subsequence thereof into a fertilized egg or a cell of an embryo of a mammal so as to incorporate the expression system into the germline of the mammal and developing the resulting injected fertilized egg or embryo into an adult female mammal. In one embodiment, the endogenous polypeptide expressing capability of the mammal is destroyed and/or replaced with the expression system defined above. The invention further relates to a transgenic non-human mammal such as a mouse, rat, rabbit, goat, sheep, pig, lama, camel or bovine species whose germ cells a somatic cells contain a DNA sequence as defined above

as a result of chromosomal incorporation into the non-human mammalian genome, or into the genome of an ancestor of said non-human mammal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 9 OF 63 USPATFULL

ACCESSION NUMBER:	2000:18625 USPATFULL			
TITLE:	Transgenic non-human mammals producing EC-SOD protein in their milk			
INVENTOR(S):	Hansson, Lennart, Bjorkvagen 50, S-902 40 Ume.ang., Sweden			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6025540		20000215	
	WO 9500637		19950105	<--
APPLICATION INFO.:	US 1995-556965		19951207	(8)
	WO 1994-IB181		19940624	
			19951207	PCT 371 date
			19951207	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	DK 1993-753	19930624

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Priebe, Scott D.
ASSISTANT EXAMINER: Wilson, Michael C.
LEGAL REPRESENTATIVE: Cooper, Iver P.
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 2719

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a transgenic non-human mammal comprising a DNA sequence encoding human extracellular superoxide dismutase (human EC-SOD) or a variant thereof which is expressed in the milk. Transgenic mice containing a chimeric whey acidic protein gene promoter operatively linked to human EC-SOD gene were produced. Levels of up to 0.7 mg human EC-SOD protein/mL milk were observed. The mammalian expression system is preferably expressed in a non-human mammal selected from the group containing rabbits, mice, rats, goats, sheep, pigs, llama, camels and bovine species. The human EC-SOD proteins dismutate superoxide radicals and bind heparin. Within the scope of the invention are also method for producing a transgenic non-human mammal capable of expressing human EC-SOD as defined above, and methods of making milk and methods of isolating protein from the milk.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 10 OF 63 USPATFULL

ACCESSION NUMBER:	1999:170432 USPATFULL			
TITLE:	Polynucleotide encoding a novel purinergic P.sub.2U receptor			
INVENTOR(S):	Coleman, Roger, Mountain View, CA, United States Au-Young, Janice, Berkeley, CA, United States Stuart, Susan G., Montara, CA, United States Guegler, Karl J., Menlo Park, CA, United States			
PATENT ASSIGNEE(S):	Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6008039		19991228	<--

APPLICATION INFO.: US 1995-459046 19950602 (8)
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hutzell, Paula K.
ASSISTANT EXAMINER: Hayes, Robert C.
LEGAL REPRESENTATIVE: Luther, Barbara J., Billings, Lucy J.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1538
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides nucleotide and amino acid sequences that identify and encode a novel purinergic P.sub.U2 receptor (PNR) expressed in human **placenta**. The present invention also provides for **antisense** molecules to the nucleotide sequences which encode PNR, expression vectors for the production of purified PNR, antibodies capable of binding specifically to PNR, hybridization probes or oligonucleotides for the detection of PNR-encoding nucleotide sequences, genetically engineered host cells for the expression of PNR, and diagnostic tests based on PNR-encoding nucleic acid molecules or antibodies produced against the polypeptide PNR.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 11 OF 63 USPATFULL
ACCESSION NUMBER: 1999:170407 USPATFULL
TITLE: Method of making lipid metabolic pathway compositions
INVENTOR(S): Gimeno, Carlos J., Boston, MA, United States
Acton, Susan, Jamaica Plain, MA, United States
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6008014		19991228	<--
APPLICATION INFO.:	US 1996-707399		19960904 (8)	

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Burke, Julie
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP, Mandragouras, Amy E.
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 4049
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the discovery of novel genes encoding Lipid Metabolic Pathway (LMP) polypeptides. Therapeutics, diagnostics and screening assays based on these molecules are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 12 OF 63 USPATFULL
ACCESSION NUMBER: 1999:166981 USPATFULL
TITLE: Methods for regulating gene expression
INVENTOR(S): Bujard, Hermann, Heidelberg, Germany, Federal Republic of
Gossen, Manfred, El Cerrito, CA, United States
PATENT ASSIGNEE(S): BASF Aktiengesellschaft, Germany, Federal Republic of (non-U.S. corporation)
BASF Bioresearch Corporation, Worcester, MA, United States (U.S. corporation)
Knoll Aktiengelellschaft, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6004941		19991221	<--
APPLICATION INFO.:	US 1995-485740		19950607 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-383754, filed on 3 Feb 1995, now patented, Pat. No. US 5789156 And a continuation-in-part of Ser. No. US 1994-275876, filed on 15 Jul 1994, now patented, Pat. No. US 5654168 which is a continuation-in-part of Ser. No. US 1994-270637, filed on 1 Jul 1994, now abandoned And a continuation-in-part of Ser. No. US 1994-260452, filed on 14 Jun 1994, now patented, Pat. No. US 5650298 which is a continuation-in-part of Ser. No. US 1993-76327, filed on 14 Jun 1993, now abandoned And a continuation-in-part of Ser. No. US 1993-76726, filed on 14 Jun 1993, now patented, Pat. No. US 5464758

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Campell, Bruce R.
ASSISTANT EXAMINER: Nguyen, Dave Trong
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 4771
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of regulating gene expression in subjects using tetracycline-responsive fusion proteins are disclosed. In one embodiment, the method involves introducing into a cell the subject a nucleic acid molecule encoding a fusion protein which activates transcription, the fusion protein comprising a first polypeptide which binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which activates transcription in eukaryotic cells; and modulating the concentration of a tetracycline, or analogue thereof, in the subject. In another embodiment, the cell further comprises a fusion protein which inhibits transcription, the fusion protein comprising a first polypeptide which binds to a tet operator sequence, operatively linked to a second polypeptide which inhibits transcription in eukaryotic cells. In yet another embodiment, the method involves obtaining a cell from a subject, introducing into the cell a first nucleic acid molecule which operatively links a gene to at least one tet operator sequence, introducing into the cell a second nucleic acid molecule encoding a fusion protein of the invention to form a modified cell, administering the modified cell to the subject and modulating the concentration of a tetracycline, or analogue thereof, in the subject. The first and second nucleic acid molecules can be linked or can be separate molecules.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 13 OF 63 USPATFULL
ACCESSION NUMBER: 1999:166819 USPATFULL
TITLE: Embryogenesis protein
INVENTOR(S): Bandman, Olga, Mountain View, CA, United States
Lal, Preeti, Sunnyvale, CA, United States
Corley, Neil C., Mountain View, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6004778		19991221	<--
APPLICATION INFO.:	US 1997-904032		19970731 (8)	

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted
PRIMARY EXAMINER: Spector, Lorraine
ASSISTANT EXAMINER: Kaufman, Claire M.
LEGAL REPRESENTATIVE: Incyte Pharmaceuticals, Inc.
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Figure(s); 11 Drawing Page(s)
LINE COUNT: 2231
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a human embryogenesis protein (EMPRO) and polynucleotides which identify and encode EMPRO. The invention also provides expression vectors, host cells, agonists, antibodies and antagonists. The invention also provides methods for treating disorders associated with expression of EMPRO.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 14 OF 63 USPATFULL
ACCESSION NUMBER: 1999:163462 USPATFULL
TITLE: Polynucleotides encoding myeloid progenitor inhibitory factor-1 (MPIF-1) and polypeptides encoded thereby
INVENTOR(S): Ruben, Steven M., Olney, MD, United States
Li, Haodong, Gaithersburg, MD, United States
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6001606		19991214	<--
APPLICATION INFO.:	US 1996-722719		19960930	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-446881, filed on 5 May 1995, now abandoned which is a continuation-in-part of Ser. No. US 1995-465682, filed on 6 Jun 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-208339, filed on 8 Mar 1994, now patented, Pat. No. US 5504003 Ser. No. Ser. No. US 1995-468775, filed on 6 Jun 1995, now abandoned And Ser. No. WO 1996-US15592, filed on 27 Sep 1996 , said Ser. No. US 465682 which is a continuation-in-part of Ser. No. US 446881 , said Ser. No. US 468775 which is a continuation-in-part of Ser. No. US 446881

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-4517P	19950929 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Mertz, Prema
LEGAL REPRESENTATIVE: Sterne, Kessler, Goldstein & Fox, P.L.L.C.
NUMBER OF CLAIMS: 74
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 53 Drawing Figure(s); 49 Drawing Page(s)
LINE COUNT: 6406
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are disclosed therapeutic compositions and methods using isolated nucleic acid molecules encoding a human myeloid progenitor inhibitory factor-1 (MPIF-1) polypeptide (previously termed MIP-3 and chemokine .beta.8(CK.beta.8 or ckb-8)); a human monocyte-colony inhibitory factor (M-CIF) polypeptide (previously termed MIP1-.gamma. and chemokine .beta.1(CK.beta.1 or ckb-1)), and a macrophage inhibitory protein-4 (MIP-4), as well as MPIF-1, M-CIF and/or MIP-4 polypeptides themselves, as are vectors, host cells and recombinant methods for producing the same.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 15 OF 63 USPATFULL

ACCESSION NUMBER: 1999:159803 USPATFULL
TITLE: Receptor tyrosine kinase
INVENTOR(S): Breitman, Martin L., Willowdale, Canada
Rossant, Janet, Toronto, Canada
Dumont, Daniel J., Oakville, Canada
Yamaguchi, Terry P., Toronto, Canada
Breitman, Jo-Ann, Toronto, Canada executor of said Martin L. Breitman, deceased
PATENT ASSIGNEE(S): Mount Sinai Hospital Corporation, Toronto, Canada (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5998187		19991207	<--
APPLICATION INFO.:	US 1997-838957		19970423 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-278089, filed on 20 Jul 1994, now patented, Pat. No. US 5687714 which is a continuation-in-part of Ser. No. US 1994-235408, filed on 29 Apr 1994, now abandoned which is a continuation-in-part of Ser. No. US 1992-921795, filed on 30 Jul 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Teng, Sally
LEGAL REPRESENTATIVE: Merchant & Gould P.C.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Figure(s); 70 Drawing Page(s)
LINE COUNT: 4316

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel receptor tyrosine kinase protein and isoforms thereof which are expressed in cells of the endothelial lineage, and DNA segments encoding the novel protein and isoforms thereof are disclosed. Methods for identifying ligands which are capable of binding to the receptor protein and methods for screening for agonist or antagonist substances of the interaction of the protein and a ligand are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 16 OF 63 USPATFULL

ACCESSION NUMBER: 1999:159786 USPATFULL
TITLE: Polynucleotides encoding hepatocyte-specific members of the FGF family
INVENTOR(S): Arakawa, Tsutomu, Thousand Oaks, CA, United States
Danilenko, Dimitry Michael, Camarillo, CA, United States
Itoh, Nobuyuki, Ohtsu, Japan
Martin, Francis Hall, Newbury Park, CA, United States
PATENT ASSIGNEE(S): Amgen Inc., Thousand Oaks, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5998170		19991207	<--
APPLICATION INFO.:	US 1997-943915		19971003 (8)	

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Feisee, Lila
ASSISTANT EXAMINER: Saoud, Christine
LEGAL REPRESENTATIVE: Mazza, Richard J., Levy, Ron K., Odre, Steven M.

NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 1898
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Nucleic acid molecules are described which are useful in vectors, transformed or transfected host cells, and methods for the recombinant expression of hepatocyte growth-specific polypeptide members of the FGF family.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 17 OF 63 USPATFULL
ACCESSION NUMBER: 1999:155514 USPATFULL
TITLE: Multidrug resistance-associated polypeptide
INVENTOR(S): Shyjan, Andrew, Nahant, MA, United States
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5994130		19991130	<--
APPLICATION INFO.:	US 1997-1273		19971231 (9)	

RELATED APPLN. INFO.: Division of Ser. No. US 1997-843459, filed on 16 Apr 1997
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Hutson, Richard
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 2956
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods are disclosed for improving the effectiveness of a chemotherapeutic regimen to eradicate multidrug-resistant transformed cells from the body of a mammal, preferably from the body of a human. The present disclosure capitalizes on the discovery of a novel multidrug-resistance associated protein (MRP), herein designated MRP-.beta.. The disclosed compositions include MRP-.alpha. nucleic acids, including probes and **antisense** oligonucleotides, MRP-.beta. polypeptides and antibodies, MRP-.beta. expressing host cells, and non-human mammals transgenic or nullizygous for MRP-.beta.. The disclosed methods include methods for attenuating aberrant MRP-.beta. gene expression, protein production and/or protein function. In addition, methods are disclosed for identifying and using a modulator, such as an inhibitor, of MRP-.beta.. Preferably, the modulator is a small molecule.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 18 OF 63 USPATFULL
ACCESSION NUMBER: 1999:151195 USPATFULL
TITLE: GATA-6 transcription factor: compositions and methods
INVENTOR(S): Walsh, Kenneth, Carlisle, MA, United States
PATENT ASSIGNEE(S): St. Elizabeth's Medical Center, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5990092		19991123	<--
APPLICATION INFO.:	US 1997-927394		19970827 (8)	

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted
PRIMARY EXAMINER: Degen, Nancy
ASSISTANT EXAMINER: Schwartzman, Robert
LEGAL REPRESENTATIVE: Wolf, Greenfield & Sacks P.C.
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 2449
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for reducing or preventing the proliferation of vascular smooth muscle cells are provided. The method involves the step of administering an isolated GATA-6 molecule to a subject to prevent or reduce vascular smooth muscle cell proliferation. The isolated GATA-6 molecule can be a GATA-6 nucleic acid or a GATA-6 protein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 19 OF 63 USPATFULL
ACCESSION NUMBER: 1999:141655 USPATFULL
TITLE: Mammalian cell death preventing kinase, DPK
INVENTOR(S): Xu, Hua, Thousand Oaks, CA, United States
PATENT ASSIGNEE(S): Amgen Inc., Thousand Oaks, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5981248		19991109	<--
APPLICATION INFO.:	US 1997-969630		19971113	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Sisson, Bradley L.
ASSISTANT EXAMINER: Bugaisky, Gabriele E.
LEGAL REPRESENTATIVE: Odre, S., Cook, R.
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Figure(s); 20 Drawing Page(s)
LINE COUNT: 2213
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are nucleic acids encoding novel proteins, designated DPK. Also disclosed are amino acid sequences for DPK polypeptides, methods for preparing DPK polypeptides, and other related aspects.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 20 OF 63 USPATFULL
ACCESSION NUMBER: 1999:132565 USPATFULL
TITLE: Diagnosis and treatment of AUR-1 and/or AUR-2 related disorders
INVENTOR(S): Plowman, Gregory, San Carlos, CA, United States
Mossie, Kevin, Gauteng, South Africa
PATENT ASSIGNEE(S): Sugen, Inc., Redwood City, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5972676		19991026	<--
APPLICATION INFO.:	US 1997-974655		19971119	(8)

RELATED APPLN. INFO.: Division of Ser. No. US 1996-755728, filed on 25 Nov 1996
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wax, Robert A.
LEGAL REPRESENTATIVE: Lyon & Lyon LLP
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1,7

LINE COUNT: 2323
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to AUR-1 and/or AUR-2 polypeptides, nucleic acids encoding such polypeptides, cells, tissues and animals containing such nucleic acids, antibodies to such polypeptides, assays utilizing such polypeptides, and methods relating to all of the foregoing. Methods for treatment, diagnosis, and screening are provided for AUR-1 and/or AUR-2 related diseases or conditions characterized by an abnormal interaction between a AUR-1 and/or AUR-2 polypeptide and a AUR-1 and/or AUR-2 binding partner.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 21 OF 63 USPATFULL
ACCESSION NUMBER: 1999:132542 USPATFULL
TITLE: Polynucleotides encoding a protein of embryogenesis
INVENTOR(S): Hillman, Jennifer L., Mountain View, CA, United States
Shah, Purvi, Sunnyvale, CA, United States
Corley, Neil C., Mountain View, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5972653		19991026	<--
APPLICATION INFO.:	US 1997-926724		19970910	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kemmerer, Elizabeth
ASSISTANT EXAMINER: Romeo, David S.
LEGAL REPRESENTATIVE: Incyte Pharmaceuticals, Inc., Streeter, David G.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 11 Drawing Page(s)
LINE COUNT: 2220
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a human protein of embryogenesis (PREM) and polynucleotides which identify and encode PREM. The invention also provides expression vectors, host cells, agonists, antibodies and antagonists. The invention also provides methods for treating disorders associated with expression of PREM.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 22 OF 63 USPATFULL
ACCESSION NUMBER: 1999:128386 USPATFULL
TITLE: Compositions and methods for the treatment and diagnosis of cardiovascular disease using rchd523 as a target
INVENTOR(S): Falb, Dean A., Wellesley, MA, United States
Gimbrone, Jr., Michael A., Jamaica Plain, MA, United States
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5968770		19991019	<--
APPLICATION INFO.:	US 1995-485573		19950607	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-386844, filed on 10 Feb 1995
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Low, Christopher S. F.

ASSISTANT EXAMINER: Nguyen, Dave Trong
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 40 Drawing Figure(s); 40 Drawing Page(s)
LINE COUNT: 5019
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods and compositions for the treatment and diagnosis of cardiovascular disease, including, but not limited to, atherosclerosis, ischemia/reperfusion, hypertension, restenosis, and arterial inflammation. Specifically, the present invention identifies and describes genes which are differentially expressed in cardiovascular disease states, relative to their expression in normal, or non-cardiovascular disease states, and/or in response to manipulations relevant to cardiovascular disease. Further, the present invention identifies and describes genes via the ability of their gene products to interact with gene products involved in cardiovascular disease. Still further, the present invention provides methods for the identification and therapeutic use of compounds as treatments of cardiovascular disease. Moreover, the present invention provides methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of cardiovascular disease, and for monitoring the efficacy of compounds in clinical trials. Additionally, the present invention describes methods for the diagnostic evaluation and prognosis of various cardiovascular diseases, and for the identification of subjects exhibiting a predisposition to such conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 23 OF 63 USPATFULL
ACCESSION NUMBER: 1999:124708 USPATFULL
TITLE: Genetic sequences encoding glucocorticoid dehydrogenases and uses thereof
INVENTOR(S): Funder, John W., North Carlton, Australia
Albiston, Anthony L., North Balwyn, Australia
Obeyesekere, Varuni R., Malvern, Australia
Krozowski, Zygmunt S., Wheelers Hill, Australia
Smith, Robin E., Murrumbeena, Australia
PATENT ASSIGNEE(S): Baker Medical Research Institute, Victoria, Australia (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5965372		19991012	<--
APPLICATION INFO.:	US 1996-754369		19961122	(8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-519081, filed on 24 Aug 1995
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Huff, Sheela
ASSISTANT EXAMINER: Eyler, Yvonne
LEGAL REPRESENTATIVE: White, John P.Cooper & Dunham LLP
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 1428
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates generally to a nucleic acid molecule encoding, or complementary to a nucleic acid molecule encoding, a recombinant NAD+ dependent glucocorticoid dehydrogenase and more particularly to 11 .beta.-hydroxysteroid dehydrogenase-2 (11 .beta.HSD2). When expressed in a prokaryotic or eukaryotic cell, the nucleic acid molecule of the present invention is used to assay for potential agonists or antagonists of glucocorticoid dehydrogenase

activity. Further, the present invention relates to immunoreactive molecules to NAD+ dependent glucocorticoid dehydrogenase which provide the basis for a new range of diagnostic agents for use, such as in the diagnosis and treatment of hypertension and in predicting the potential outcome of in vitro fertilisation and embryo transfer procedures.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 24 OF 63 USPATFULL

ACCESSION NUMBER: 1999:121224 USPATFULL
TITLE: Methods for modulation of cholesterol transport
INVENTOR(S): Kozarsky, Karen, Philadelphia, PA, United States
Rigotti, Attilio, Malden, MA, United States
Krieger, Monty, Needham, MA, United States
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, Cambridge, MA, United States (U.S. corporation)
The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5962322		19991005	<--
APPLICATION INFO.:	US 1996-749907		19961115	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Low, Christopher S. F.
LEGAL REPRESENTATIVE: Arnall Golden & Gregory, LLP
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1762
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for regulation of lipid and cholesterol uptake are described which are based on regulation of the expression or function of the SR-BI HDL receptor. The examples demonstrate that estrogen dramatically downregulates SR-BI under conditions of tremendous upregulation of the LDL-receptor. The examples also demonstrate the upregulation of SR-BI in rat adrenal membranes and other non-placental steroidogenic tissues from animals treated with estrogen, but not in other non-placental non-steroidogenic tissues, including lung, liver, and skin. Examples further demonstrate the uptake of fluorescently labeled HDL into the liver cells of animal, which does not occur when the animals are treated with estrogen. Examples also demonstrate the in vivo effects of SR-BI expression on HDL metabolism, in mice transiently overexpressing hepatic SR-BI following recombinant adenovirus infection. Overexpression of the SR-BI in the hepatic tissue caused a dramatic decrease in cholesterol blood levels. These results demonstrate that modulation of SR-BI levels, either directly or indirectly, can be used to modulate levels of cholesterol in the blood.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 25 OF 63 USPATFULL

ACCESSION NUMBER: 1999:121216 USPATFULL
TITLE: Calcium receptor-active molecules
INVENTOR(S): Brown, Edward M., Milton, MA, United States
Hebert, Steven C., Wellesley, MA, United States
Garrett, Jr., James E., Salt Lake City, UT, United States
PATENT ASSIGNEE(S): NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)
Brigham and Women's Hospital, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5962314		19991005	<--
APPLICATION INFO.:	US 1997-943986		19971003	(8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-484565, filed on 7 Jun 1995, now patented, Pat. No. US 5763569 which is a continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994 which is a continuation-in-part of Ser. No. WO 1994-US12117, filed on 21 Oct 1994 Ser. No. Ser. No. US 1994-292827, filed on 19 Aug 1994, now abandoned Ser. No. Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned And Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ulm, John
ASSISTANT EXAMINER: Saoud, Christine
LEGAL REPRESENTATIVE: Lyon & Lyon LLP
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 111 Drawing Figure(s); 85 Drawing Page(s)
LINE COUNT: 7882
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca.sup.2+ and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 26 OF 63 USPATFULL

ACCESSION NUMBER: 1999:121214 USPATFULL
TITLE: Diagnosis and treatment of AUR-1 and/or AUR-2 related disorders
INVENTOR(S): Plowman, Gregory, San Carlos, CA, United States
Mossie, Kevin, Gauteng, South Africa
PATENT ASSIGNEE(S): Sugen, Inc., Redwood City, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5962312		19991005	<--
APPLICATION INFO.:	US 1996-755728		19961125	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Lau, Kawai
LEGAL REPRESENTATIVE: Lyon & Lyon LLP
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 2310
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to AUR-1 and/or AUR-2 polypeptides, nucleic acids encoding such polypeptides, cells, tissues and animals containing such nucleic acids, antibodies to such polypeptides, assays

utilizing such polypeptides, and methods relating to all of the foregoing. Methods for treatment, diagnosis, and screening are provided for AUR-1 and/or AUR-2 related diseases or conditions characterized by an abnormal interaction between a AUR-1 and/or AUR-2 polypeptide and a AUR-1 and/or AUR-2 binding partner.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 27 OF 63 USPATFULL
ACCESSION NUMBER: 1999:113643 USPATFULL
TITLE: Chromosome 18 marker
INVENTOR(S): Chen, Hong, Brookline, MA, United States
Freimer, Nelson B., San Francisco, CA, United States
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)
The Regents University of California, Oakland, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5955355		19990921	<--
APPLICATION INFO.:	US 1997-828010		19970327	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-14498P	19960328 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hutzell, Paula K.
ASSISTANT EXAMINER: Pellegrino, Susan
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 2973
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the mammalian fsh05 gene, a novel gene associated with bipolar affective disorder (BAD) in humans. The invention encompasses fsh05 nucleic acids, recombinant DNA molecules, cloned genes or degenerate variants thereof, fsh05 gene products and antibodies directed against such gene products, cloning vectors containing mammalian fsh05 gene molecules, and hosts that have been genetically engineered to express such molecules. The invention further relates to methods for the identification of compounds that modulate the expression of fsh05 and to using such compounds as therapeutic agents in the treatment of fsh05 disorders and neuropsychiatric disorders. The invention also relates to methods for the diagnostic evaluation, genetic testing and prognosis of fsh05 disorders and neuropsychiatric disorders including schizophrenia, attention deficit disorder, a schizoaffective disorder, a bipolar affective disorder or a unipolar affective disorder, and to methods and compositions for the treatment these disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 28 OF 63 USPATFULL
ACCESSION NUMBER: 1999:113594 USPATFULL
TITLE: Genes encoding proteins that interact with the tub protein
INVENTOR(S): Gimeno, Carlos J., Wellesley, MA, United States
Errada, Patrick R., Cambridge, MA, United States
PATENT ASSIGNEE(S): Millenium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5955306		19990921	<--
APPLICATION INFO.:	US 1997-897340		19970721	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-715032, filed on 17 Sep 1996, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Railey, II, Johnny F.
LEGAL REPRESENTATIVE: Hanley, Elizabeth A., Mandragouras, Amy E.Lahive & Cockfield, LLP
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 4240
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the discovery of novel genes encoding Tub interactor (TI) polypeptides. Therapeutics, diagnostics and screening assays based on these molecules are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 29 OF 63 USPATFULL
ACCESSION NUMBER: 1999:99644 USPATFULL
TITLE: Methods and compositions for multiple gene transfer into bone cells
INVENTOR(S): Bonadio, Jeffrey, Ann Harbor, MI, United States
Goldstein, Steven A., Ann Harbor, MI, United States
PATENT ASSIGNEE(S): The Regent of The University of Michigan, Ann Arbor, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5942496		19990824	<--
APPLICATION INFO.:	US 1994-316650		19940930	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-199780, filed on 18 Feb 1994, now patented, Pat. No. US 5763416
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Campell, Bruce R.
ASSISTANT EXAMINER: Nguyen, Dave Trong
LEGAL REPRESENTATIVE: Arnold White & Durkee
NUMBER OF CLAIMS: 130
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 26 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 5310
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are methods, compositions, kits and devices for use in transferring nucleic acids into bone cells in situ and/or for stimulating bone progenitor cells. Type II collagen and, particularly, osteotropic genes, are shown to stimulate bone progenitor cells and to promote bone growth, repair and regeneration in vivo. Gene transfer protocols are disclosed for use in transferring various nucleic acid materials into bone, as may be used in treating various bone-related diseases and defects including fractures, osteoporosis, osteogenesis imperfecta and in connection with bone implants.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 30 OF 63 USPATFULL
ACCESSION NUMBER: 1999:99565 USPATFULL
TITLE: CD44-like protein and nucleic acids
INVENTOR(S): Ni, Jian, Rockville, MD, United States
Gentz, Reiner L., Silver Spring, MD, United States
Dillon, Patrick J., Gaithersburg, MD, United States

PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5942417		19990824	<--
APPLICATION INFO.:	US 1997-892880		19970715	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-21762P	19960715 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Horlick, Kenneth R.
LEGAL REPRESENTATIVE: Sterne, Kessler, Goldstein & Fox P.L.L.C.
NUMBER OF CLAIMS: 87
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 3185
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention concerns a novel CD44-like protein receptor. In particular, isolated nucleic acid molecules are provided encoding the CD44-like protein. CD44-like polypeptides are also provided, as are screening methods for identifying agonists and antagonists capable of enhancing or inhibiting CD44-like protein-mediated signaling. The invention further concerns therapeutic methods for treating diseases associated with processes mediated by CD44-like protein signaling.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l12 ibib kwic 1-10

L12 ANSWER 1 OF 63 MEDLINE
ACCESSION NUMBER: 1998364972 MEDLINE
DOCUMENT NUMBER: 98364972 PubMed ID: 9701242
TITLE: **Thrombin receptor** overexpression in malignant and physiological invasion processes.
AUTHOR: Even-Ram S; Uziely B; Cohen P; Grisaru-Granovsky S; Maoz M; Ginzburg Y; Reich R; Vlodavsky I; Bar-Shavit R
CORPORATE SOURCE: Department of Oncology, Hadassah-Hebrew University Hospital, Jerusalem, Israel.
SOURCE: NATURE MEDICINE, **(1998 Aug)** 4 (8) 909-14.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
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TI **Thrombin receptor** overexpression in malignant and physiological invasion processes.
SO NATURE MEDICINE, **(1998 Aug)** 4 (8) 909-14.
Journal code: 9502015. ISSN: 1078-8956.
AB . . . metastasis is well recognized, the role of proteolytically activated cell surface receptors has not been elucidated. We report here that **thrombin receptor**, a member of the protease-activated receptor family, is preferentially expressed in highly metastatic human breast carcinoma cell lines and breast carcinoma biopsy specimens. Introduction of **thrombin receptor antisense** cDNA considerably inhibited the invasion of metastatic breast carcinoma cells in culture through a reconstituted basement

membrane. During placental **implantation** of the human embryo, **thrombin receptor** is transiently expressed in the invading cytotrophoblasts. These results emphasize the involvement of **thrombin receptor** in cell invasion associated with tumor progression and normal embryonic development.

CT . . .

ME, metabolism

Breast Neoplasms: ME, metabolism
*Breast Neoplasms: PA, pathology
Carcinoma: PA, pathology
Carcinoma, Infiltrating Duct: PA, pathology
Cell Line
***DNA, Antisense: PD, pharmacology**
DNA, Complementary
Gene Expression Regulation
Neoplasm Invasiveness
Neoplasm Metastasis: PA, pathology
Neoplasm Metastasis: PC, prevention & control
Ovum Implantation
***Placenta: PH, physiology**
Pregnancy
*Receptors, Thrombin: BI, biosynthesis
Receptors, Thrombin: PH, physiology
Recombinant Proteins: BI, biosynthesis
Transfection
Trophoblast: PH, physiology
Tumor. . .

CN 0 (DNA, **Antisense**); 0 (DNA, Complementary); 0 (Receptors, Thrombin); 0 (Recombinant Proteins)

L12 ANSWER 2 OF 63 USPATFULL

ACCESSION NUMBER: 2002:303979 USPATFULL

TITLE: Use of neomycin for treating angiogenesis-related diseases

INVENTOR(S): Hu, Guo-fu, Brookline, MA, United States
Vallee, Bert L., Boston, MA, United States

PATENT ASSIGNEE(S): Endowment for Research in Human Biology, Inc., Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6482802	B1	20021119	
	WO 9958126		19991118	<--
APPLICATION INFO.:	US 2000-700436		20001109	(9)
	WO 1999-US10269		19990511	
			20001109	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-84921P	19980511 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Raymond, Richard L.
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 63
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 2312

PI US 6482802 B1 20021119
WO 9958126 19991118 <--

SUMM . . . development, development and growth of normal tissues and organs, wound healing, and the formation of the corpus luteum, endometrium and **placenta**.

SUMM . . . include the C-terminal peptides of angiogenin (Rybak et al.,

1989, Biochem. Biophys. Res. Comm. 162:535-543), the ribonuclease inhibitor from human **placenta** (Lee et al., 1988, Biochemistry 27:8545-8553, Shapiro et al., 1987, Proc. Natl. Acad Sci. USA 84:2238-2241) and, more recently, a. . .

DETD . . . Proc. Natl. Acad. Sci. USA 84:2238-2241); actin and fragments thereof that interferes with angiogenin interaction with its receptor, such as NH.sub.2-Tyr-Ser-Val-Trp-Ile-Gly-Gly-Ser-Ile-Leu-Ala-Ser-Leu-Ser-**Thr**-Phe-Gln-Gln-Met-Trp-Ile-Ser-Lys-COOH (SEQ ID NO: 4) and derivatives thereof (Hu et al., Proc. Natl. Acad. Sci. USA 90:1217-1221); nucleotides that inhibit the. . .

DETD Compositions of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by **implantation** (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric. . .

DETD . . . in athymic mice has been used extensively to show that angiogenin antagonists such as monoclonal antibodies, its binding protein and **antisense** DNA, prevent the establishment of human tumor cells in mice (Olson et al., 1998, Proc. Am. Assoc. Cancer Res. 39:665A;. . .

DETD

GENERAL INFORMATION:

NUMBER OF SEQ ID NOs: 5

SEQUENCE CHARACTERISTICS:

SEQ ID NO: 1

LENGTH: 11

TYPE: PRT

ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: deduced from **antisense** RNA corresponding to the receptor-binding stie of angiogenin in 5'->3' direction

SEQUENCE: 1

Val Phe Ser Val Arg Val Ser Ile Leu Val Phe
1 5 10

SEQUENCE CHARACTERISTICS:

SEQ ID NO: 2

LENGTH: 13

TYPE: PRT

ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: deduced from **antisense** RNA corresponding to the receptor-binding stie of angiogenin in 3'->5' direction

SEQUENCE: 2

Leu Leu Phe Leu Pro Leu Gly Val Ser. . . NO: 4

LENGTH: 23

TYPE: PRT

ORGANISM: Homo Sapiens

SEQUENCE: 4

Tyr Ser Val Trp Ile Gly Gly Ser Ile Leu Ala Ser Leu Ser **Thr** Phe
1 5 10 15

Gln Gln Met Trp Ile Ser Lys
20

SEQUENCE CHARACTERISTICS:

SEQ ID NO: 5

LENGTH: 44

TYPE: DNA

ORGANISM: Homo Sapiens

SEQUENCE:. . .

CLM What is claimed is:

. . . ID NO. 1), peptide comprising the sequence NH.sub.2-Leu-Leu-Phe-Leu-Pro-Leu-Gly-Val-Ser-Leu-Leu-Asp-Ser-COOH (SEQ ID NO. 2), human placental ribonuclease inhibitor, peptide comprising the sequence NH.sub.2-Tyr-Ser-Val-Trp-Ile-Gly-Gly-Ser-Ile-Leu-Ala-Ser-Leu-Ser-**Thr**-Phe-Gln-Gln-Met-Trp-Ile-Ser-Lys-COOH (SEQ ID NO. 4), peptide

comprising the sequence NH.sub.2-Ala-Gln-Leu-Ala-Gly-Glu-Cys-Arg-Glu-Asn-Val-Cys-Met-Gly-Ile-Glu-Gly-Arg-COOH (SEQ ID NO. 3), nucleotide comprising the sequence 5'-CGGACGAATGCTTTGATGTTGTGCTGGACCAGCGTTCATTCTCA-3' (SEQ ID. . .
. . . ID NO. 1), peptide comprising the sequence NH.sub.2-Leu-Leu-Phe-Leu-Pro-Leu-Gly-Val-Ser-Leu-Leu-Asp-Ser-COOH (SEQ ID NO. 2), human placental ribonuclease inhibitor, peptide comprising the sequence NH.sub.2-Tyr-Ser-Val-Trp-Ile-Gly-Gly-Ser-Ile-Leu-Ala-Ser-Leu-Ser-**Thr**-Phe-Gln-Gln-Met-Trp-Ile-Ser-Lys-COOH (SEQ ID NO. 4), peptide comprising the sequence NH.sub.2-Ala-Gln-Leu-Ala-Gly-Glu-Cys-Arg-Glu-Asn-Val-Cys-Met-Gly-Ile-Glu-Gly-Arg-COOH (SEQ ID NO. 3), nucleotide comprising the sequence 5'-CGGACGAATGCTTTGATGTTGTGCTGGACCAGCGTTCATTCTCA-3'(SEQ ID NO.. . .

L12 ANSWER 3 OF 63 USPATFULL

ACCESSION NUMBER:	2002:160542 USPATFULL
TITLE:	Method of screening for a modulator of angiogenesis
INVENTOR(S):	Lau, Lester F., Chicago, IL, United States
PATENT ASSIGNEE(S):	Munin Corporation, Chicago, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 6413735	B1	20020702		
	WO 9733995		19970918		<--
APPLICATION INFO.:	US 1999-142569		19990402	(9)	
	WO 1997-US4193		19970314		
			19990402	PCT 371 date	

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1996-13958P	19960315	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Crouch, Deborah
ASSISTANT EXAMINER:	Woitach, Joseph T.
LEGAL REPRESENTATIVE:	Katten Muchin Zavis
NUMBER OF CLAIMS:	9
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT:	4088

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 6413735 B1 20020702
WO 9733995 19970918 <--

SUMM . . . be induced by a variety of techniques including, but not limited to, the administration of chemicals, e.g., carcinogens, and the **implantation** of cancer cells. A related aspect of the invention is a method for treating a solid tumor comprising the step. . .

SUMM . . . the vascularization of grafts, e.g., skin grafts. Another method of the invention is directed to a process for promoting bone **implantation**, including bone grafts. The method for promoting bone **implantation** comprises the step of contacting a bone implant or receptive site with a biologically effective (i.e., chondrogenically effective) amount of. . . to a biocompatible wrap such as a biodegradable gauze and contacting the wrap with a bone implant, thereby promoting bone **implantation**. The bone implants comprise natural bones and fragments thereof, as well as inanimate natural and synthetic materials that are biocompatible,. . .

DETD . . . cyr61 mRNA expression pattern was determined using an RNase protection technique. O'Brien et al., (1992). In particular, a 289 nucleotide **antisense** riboprobe was used that would protect 246 nucleotides of the murine cyr61 mRNA (nucleotides 67 to 313 using the numbering. . .

DETD . . . according to the manufacturer's instructions. The results

showed that cyr61 mRNA is abundant in the human heart, lung, pancreas, and **placenta**; is present at low levels in skeletal muscle, kidney and brain; and is not detectable in liver. These results are. . .

DETD . . . lines 10-29, incorporated herein by reference. A 2.4 kb RNA was identified. The expression of CTGF was high in the **placenta**, lung, heart, kidney, skeletal muscle and pancreas. However, CTGF expression was low in the liver and brain.

DETD . . . Fisp12 was determined. Cyr61 and Fisp12 were co-localized in a number of tissues and organs. A notable example is the **placenta** , where both proteins were readily detectable. In particular, both Cyr61 and Fisp12 were found in and around the trophoblastic giant. . .

DETD In addition to the **placenta**, both Cyr61 and Fisp12 were detected in the cardiovascular system, including the smooth muscle, the cardiomyocytes, and the endothelia. Both. . .

DETD In summary, Cyr61 and Fisp12 have been co-localized in the **placenta** the cardiovascular system, the lung and the skin. Neither protein was detected in the digestive system or the endocrine glands.. . .

DETD . . . described (Polverini, et al., J. Immunol. 118.529-532 [1977]). Sponge implants were evaluated at days 5, 7, 10, and 14 after **implantation**. Thirty minutes before sacrifice, mice were injected with a solution containing [.sup.3H]-thymidine in saline (specific activity 6.7 Ci/mM; New England. . .

DETD . . . vivo, to a sponge laden with Cyr61 in the presence or absence of a suspected modulator of Cyr61 activity. Following **implantation**, incubation, and removal, the relative rates of cell migration are determined. A promoter of Cyr61 activity will increase the rate. . .

DETD To provide slow release of the protein after **implantation** in the cornea, protein is mixed with poly-2-hydroxyethylmethacrylate (Hydron), or an equivalent agent, to form a pellet of approximately 5. . . made in this way are rehydrated with a drop of sterile lactated Ringers solution and implanted as described above. After **implantation**, the corneal pocket is sealed with erythromycin ointment. After **implantation**, the protein-Hydron pellet should remain near the limbus of the cornea (cornea-sclera border) and vision should not be significantly impaired.

DETD . . . frequently are treated by the introduction of a prosthesis e.g., hip prosthesis, knee prosthesis. Beyond questions of histocompatibility, the successful **implantation** of a prosthetic device requires that the foreign element become integrated into the organism's skeletal structure. The capacity of Cyr61. . . to induce the differentiation of mesenchyme cells into chondrocytes, should prove valuable in the treatment of skeletal disorders by prosthesis **implantation**. For example, integration of a prosthetic device by chondrocyte colonization would be promoted by therapeutic treatments involving the administration of. . .

DETD . . . 179

```
ATG AGC TCC AGC ACC TTC AGG ACG CTC GCT GTC GCC GTC ACC CTT CTC      227
Met Ser Ser Ser Thr Phe Arg Thr Leu Ala Val Ala Val
       Thr Leu Leu
  1               5                  10                  15

CAC TTG ACC AGA CTG GCG CTC TCC ACC TGC CCC GCC GCC TGC CAC TGC      275
His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ala Cys His
       Cys
             20                  25                  30

CCT CTG GAG GCA CCC AAG TGC GCC CCG GGA GTC. . . 50                  55
       60

AGC AAA ACT CAG CCC TGC GAC CAC ACC AAG GGG TTG GAA TGC AAT TTC      419
Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn
       Phe
 65                  70                  75                  80

GGC GCC AGC TCC ACC GCT CTG AAA GGG ATC TGC AGA GCT CAG TCA GAA      467
```

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Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu
                  85                  90                  95
GGC AGA CCC TGT GAA TAT AAC.  .  .  AAA CAC CAG TGC ACA TGT ATT GAT GGC GCC GTG
       563
Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val
        115                 120                 125
GGC TGC ATT CCT CTG TGT CCC CAA GAA CTG TCT CTC.  .  .  GAG GTG GAG TTA ACG AGA
      AAC AAT      755
Asp Leu Leu Gly Leu Asp Ala Ser Glu Val Glu Leu Thr Arg Asn Asn
            180                 185                 190
GAG TTA ATC GCA ATT GGA AAA GGC AGC TCA CTG AAG AGG CTT CCT.  .  .  195
       200                 205
TTT GGC ACC GAA CCG CGA GTT CTT TTC AAC CCT CTG CAC GCC CAT GGC       851
Phe Gly Thr Glu Pro Arg Val Leu Phe Asn Pro Leu His Ala His Gly
    210                 215                 220
CAG AAA TGC ATC GTT CAG ACC ACG TCT TGG TCC CAG TGC TCC AAG AGC       899
Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser Lys
       Ser
225                 230                 235                 240
TGC GGA ACT GGC ATC TCC ACA CGA GTT ACC AAT GAC AAC CCA GAG TGC       947
Cys Gly Thr Gly Ile Ser Thr Arg Val Thr Asn Asp
      Asn Pro Glu Cys
                245                 250                 255
CGC CTG GTG AAA GAG ACC CGG ATC TGT GAA GTG CGT CCT TGT GGA CAA       995
Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro Cys Gly Gln
            260                 265                 270
CCA GTG TAC AGC AGC CTA AAA AAG.  .  .  AAA TGC AGC AAG ACC AAG      1043
Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys Thr Lys
        275                 280                 285
AAA TCC CCA GAA CCA GTC AGA TTT ACT TAT GCA GGA TGC TCC AGT GTC      1091
Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly Cys Ser Ser Val
    290                 295                 300
AAG AAA TAC CGG CCC AAA TAC TGC GGC TCC TGC.  .  .  Cys
305                 310                 315                 320
TGC ACA CCT CTG CAG ACC AGA ACT GTG AAG ATG CGG TTC CGA TGC GAA      1187
Cys Thr Pro Leu Gln Thr Arg Thr Val Lys Met Arg
       Phe Arg Cys Glu
                325                 330                 335
GAT GGA GAG ATG TTT TCC AAG AAT GTC ATG.  .  .  CHARACTERISTICS:
LENGTH: 379 amino acids
TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: protein
FEATURE:
NAME/KEY: misc_feature
OTHER INFORMATION:   "Mouse Cyr61 amino acid sequence"
SEQUENCE:  2
Met Ser Ser Ser Thr Phe Arg Thr Leu Ala Val Ala Val
       Thr Leu Leu
  1               5                  10                  15
His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ala Cys His
       Cys
             20                  25                  30
Pro Leu Glu Ala Pro Lys Cys Ala Pro Gly Val.  .  .  45
Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu Asp Cys
     50                  55                  60
Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn
       Phe
 65                  70                  75                  80
Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu
                  85                  90                  95
Gly Arg Pro Cys Glu Tyr Asn.  .  .  Ser Arg Ile Tyr Gln Asn Gly Glu Ser
            100                 105                 110
Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val
```

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        115                 120                 125
Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu.  .  .  Ser Leu Asp Asp Gln Asp
                165                 170                 175
Asp Leu Leu Gly Leu Asp Ala Ser Glu Val Glu Leu Thr Arg Asn Asn
            180                 185                 190
Glu Leu Ile Ala Ile Gly Lys Gly Ser Ser Leu Lys Arg Leu Pro Val
        195                 200                 205
Phe Gly Thr Glu Pro Arg Val Leu Phe Asn Pro Leu His Ala His Gly
    210                 215                 220
Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser Lys
       Ser
225                 230                 235                 240
Cys Gly Thr Gly Ile Ser Thr Arg Val Thr Asn Asp
       Asn Pro Glu Cys
                245                 250                 255
Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro Cys Gly Gln
            260                 265                 270
Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys Thr Lys
        275                 280                 285
Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly Cys Ser Ser Val
    290                 295                 300
Lys Lys Tyr Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly Arg Cys
305                 310                 315                 320
Cys Thr Pro Leu Gln Thr Arg Thr Val Lys Met Arg
       Phe Arg Cys Glu
                325                 330                 335
Asp Gly Glu Met Phe Ser Lys Asn Val Met.  .  .  GCC TTA GTC GTC ACC CTT
       168
    Met Ser Ser Arg Ile Ala Arg Ala Leu Ala Leu Val Val Thr Leu
      1                 5                  10                  15
CTC CAC TTG ACC AGG CTG GCG CTC TCC ACC TGC CCC GCT GCC TGC CAC      216
Leu His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ala Cys
       His
                20                  25                  30
TGC CCC CTG GAG GCG CCC AAG TGC GCG CCG GGA GTC.  .  .  55                  60
TGC AGC AAA ACG CAG CCC TGC GAC CAC ACC AAG GGG CTG GAA TGC AAC      360
Cys Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys
       Asn
     65                  70                  75
TTC GGC GCC AGC TCC ACC GCT CTG AAG GGG ATC TGC AGA GCT CAG TCA      408
Phe Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser
 80                  85                  90                  95
GAG GGC AGA CCC TGT GAA TAT.  .  .  CAA CAT CAG TGC ACA TGT ATT GAT GGC GCC
       504
Ser Phe Gln Pro Asn Cys Gln His Gln Cys Thr Cys Ile Asp Gly Ala
            115                 120                 125
GTG GGC TGC ATT CCT CTG TGT CCC CAA GAA CTA TCT CTC.  .  .  CTG GTC AAA GTT ACC
       GGG CAG TGC TGC GAG      600
Gly Cys Pro Asn Pro Arg Leu Val Lys Val Thr Gly Gln Cys Cys Glu
    145                 150                 155
GAG TGG GTC TGT GAC GAG GAT AGT ATC AAG GAC CCC ATG.  .  .  Glu
                180                 185                 190
TTG ACG AGA AAC AAT GAA TTG ATT GCA GTT GGA AAA GGC AGA TCA CTG      744
Leu Thr Arg Asn Asn Glu Leu Ile Ala Val Gly Lys Gly Arg Ser Leu
            195                 200                 205
AAG CGG CTC CCT.  .  .  TGT ATT GTT CAA ACA ACT TCA TGG TCC CAG TGC      840
Leu Gln Gly Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln
       Cys
    225                 230                 235
TCA AAG ACC TGT GGA ACT GGT ATC TCC ACA CGA GTT ACC AAT GAC AAC      888
Ser Lys Thr Cys Gly Thr Gly Ile Ser Thr Arg Val
       Thr Asn Asp Asn
240                 245                 250                 255
CCT GAG TGC CGC CTT GTG AAA GAA ACC CGG ATT TGT GAG GTG CGG CCT      936
```

Pro Glu Cys Arg Leu Val Lys Glu **Thr** Arg Ile Cys Glu Val Arg Pro
260 265 270
TGT GGA CAG CCA GTG TAC AGC AGC CTG AAA AAG. . . Ser
275 280 285
AAG ACC AAG AAA TCC CCC GAA CCA GTC AGG TTT ACT TAC GCT GGA TGT 1032
Lys **Thr** Lys Lys Ser Pro Glu Pro Val Arg Phe **Thr** Tyr Ala Gly
Cys
290 295 300
TTG AGT GTG AAG AAA TAC CGG CCC AAG TAC TGC GGT TCC TGC. . . 315
GGC CGA TGC TGC ACG CCC CAG CTG ACC AGG ACT GTG AAG ATG CGG TTC 1128
Gly Arg Cys Cys **Thr** Pro Gln Leu **Thr** Arg **Thr** Val
Lys Met Arg Phe
320 325 330 335
CGC TGC GAA GAT GGG GAG ACA TTT TCC AAG AAC GTC ATG ATG ATC CAG 1176
Arg Cys Glu Asp Gly Glu **Thr** Phe Ser Lys Asn Val Met Met Ile Gln
340 345 350
TCC TGC AAA TGC AAC TAC AAC TGC CCG. . . misc_feature
OTHER INFORMATION: "Human Cyr61 amino acid sequence"
SEQUENCE: 4
Met Ser Ser Arg Ile Ala Arg Ala Leu Ala Leu Val Val **Thr** Leu Leu
1 5 10 15
His Leu **Thr** Arg Leu Ala Leu Ser **Thr** Cys Pro Ala Ala Cys His
Cys
20 25 30
Pro Leu Glu Ala Pro Lys Cys Ala Pro Gly Val. . . 45
Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu Asp Cys
50 55 60
Ser Lys **Thr** Gln Pro Cys Asp His **Thr** Lys Gly Leu Glu Cys Asn
Phe
65 70 75 80
Gly Ala Ser Ser **Thr** Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu
85 90 95
Gly Arg Pro Cys Glu Tyr Asn. . . Ser Arg Ile Tyr Gln Asn Gly Glu Ser
100 105 110
Phe Gln Pro Asn Cys Gln His Gln Cys **Thr** Cys Ile Asp Gly Ala Val
115 120 125
Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly
130 135 140
Cys Pro Asn Pro Arg Leu Val Lys Val **Thr** Gly Gln Cys Cys Glu Glu
145 150 155 160
Trp Val Cys Asp Glu Asp Ser Ile Lys Asp Pro Met. . . 165 170
175
Gly Leu Leu Gly Lys Glu Leu Gly Phe Asp Ala Ser Glu Val Glu Leu
180 185 190
Thr Arg Asn Asn Glu Leu Ile Ala Val Gly Lys Gly Arg Ser Leu Lys
195 200 205
Arg Leu Pro. . . Met Glu Pro Arg Ile Leu Tyr Asn Pro Leu
210 215 220
Gln Gly Gln Lys Cys Ile Val Gln **Thr** **Thr** Ser Trp Ser Gln Cys
Ser
225 230 235 240
Lys **Thr** Cys Gly **Thr** Gly Ile Ser **Thr** Arg Val
Thr Asn Asp Asn Pro
245 250 255
Glu Cys Arg Leu Val Lys Glu **Thr** Arg Ile Cys Glu Val Arg Pro Cys
260 265 270
Gly Gln Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys
275 280 285
Thr Lys Lys Ser Pro Glu Pro Val Arg Phe **Thr** Tyr Ala Gly Cys
Leu
290 295 300
Ser Val Lys Lys Tyr Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly
305 310 315 320
Arg Cys Cys **Thr** Pro Gln Leu **Thr** Arg **Thr** Val Lys

Met Arg Phe Arg
325 330 335
Cys Glu Asp Gly Glu **Thr** Phe Ser Lys Asn Val Met Met Ile Gln Ser
340 345 350
Cys Lys Cys Asn Tyr Asn Cys Pro. . . Leu Ala Ser Val Ala Gly Pro Ile Ser Leu
Ala Leu Val Leu Leu
1 5 10 15
Ala Leu Cys **Thr** Arg Pro Ala **Thr** Gly Gln Asp Cys Ser Ala Gln
Cys
20 25 30
Gln Cys Ala Ala Glu Ala Ala Pro His Cys. . . Leu Asp Gly Cys Gly Cys Cys Arg
Val Cys Ala Lys Gln Leu Gly
50 55 60
Glu Leu Cys **Thr** Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu Phe
65 70 75 80
Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys **Thr** Ala
85 90 95
Lys Asp Gly Ala Pro Cys Val Phe Gly Gly Ser Val Tyr Arg Ser Gly
100 105 110
Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys **Thr** Cys Leu Asp Gly
115 120 125
Ala Val Gly Cys Val Pro Leu Cys Ser Met Asp Val Arg Leu. . . Lys Leu Pro Gly
Lys Cys Cys
145 150 155 160
Lys Glu Trp Val Cys Asp Glu Pro Lys Asp Arg **Thr** Ala Val Gly Pro
165 170 175
Ala Leu Ala Ala Tyr Arg Leu Glu Asp **Thr** Phe Gly Pro Asp Pro
Thr
180 185 190
Met Met Arg Ala Asn Cys Leu Val Gln **Thr Thr** Glu Trp Ser Ala
Cys
195 200 205
Ser Lys **Thr** Cys Gly Met Gly Ile Ser **Thr** Arg Val **Thr**
Asn Asp Asn
210 215 220
Thr Phe Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg Pro
225 230 235 240
Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys Ile
245 250 255
Arg **Thr** Pro Lys Ile Ala Lys Pro Val Lys Phe Glu Leu Ser Gly Cys
260 265 270
Thr Ser Val Lys **Thr** Tyr Arg Ala Lys Phe Cys Gly Val Cys
Thr Asp
275 280 285
Gly Arg Cys Cys **Thr** Pro His Arg **Thr Thr**
Thr Leu Pro Val Glu Phe
290 295 300
Lys Cys Pro Asp Gly Glu Ile Met Lys Lys Asn Met Met Phe Ile Lys
305 310 315 320
Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe Glu
325 330 335
Ser Leu Tyr. . .
DETD . . . ATGTGGTAGC TCACG 2075
SEQUENCE CHARACTERISTICS:
LENGTH: 349 amino acids
TYPE: amino acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: protein
FEATURE:
NAME/KEY: misc_feature
OTHER INFORMATION: "CTGF amino acid sequence"
SEQUENCE: 8
Met **Thr** Ala Ala Ser Met Gly Pro Val Arg Val Ala Phe Val Val Leu

1 5 10 15
Leu Ala Leu Cys. . . Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu
50 55 60
Gly Glu Leu Cys **Thr** Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
65 70 75 80
Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys **Thr**
85 90 95
Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly **Thr** Val Tyr Arg Ser
100 105 110
Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys **Thr** Cys Leu Asp
115 120 125
Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu. . . Lys Leu Pro
Gly Lys Cys
145 150 155 160
Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln **Thr** Val Val Gly
165 170 175
Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp **Thr** Phe Gly Pro Asp Pro
180 185 190
Thr Met Ile Arg Ala Asn Cys Leu Val Gln **Thr** **Thr**
Glu Trp Ser Ala
195 200 205
Cys Ser Lys **Thr** Cys Gly Met Gly Ile Ser **Thr** Arg Val
Thr Asn Asp
210 215 220
Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
225. . . 240
Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
245 250 255
Ile Arg **Thr** Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly
260 265 270
Cys **Thr** Ser Met Lys **Thr** Tyr Arg Ala Lys Phe Cys Gly Val Cys
Thr
275 280 285
Asp Gly Arg Cys Cys **Thr** Pro His Arg **Thr** **Thr**
Thr Leu Pro Val Glu
290 295 300
Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Asn Met Met Phe Ile
305 310 315 320
Lys **Thr** Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe
325 330 335
Glu Ser Leu Tyr. . . Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu
Asp
1 5 10 15
Cys Ser Lys **Thr** Gln
20
SEQUENCE CHARACTERISTICS:
LENGTH: 21 amino acids
TYPE: amino acid
STRANDEDNESS: not relevant
TOPOLOGY: not relevant
MOLECULE TYPE: peptide
SEQUENCE: 14
Pro Asn Cys Lys His Gln Cys **Thr** Cys Ile Asp Gly Ala Val Gly Cys
1 5 10 15
Ile Pro Leu Cys Pro
20
SEQUENCE CHARACTERISTICS:
LENGTH: 24 amino acids
TYPE: amino acid
STRANDEDNESS: not relevant
TOPOLOGY: not relevant
MOLECULE TYPE: peptide
SEQUENCE: 15
Cys Ile Val Gln **Thr** **Thr** Ser Trp Ser Gln Cys Ser Lys Ser Cys

Gly
1 5 10 15
Thr Gly Ile Ser **Thr** Arg Val **Thr**
20

SEQUENCE CHARACTERISTICS:
LENGTH: 26 amino acids
TYPE: amino acid
STRANDEDNESS: not relevant
TOPOLOGY: not relevant
MOLECULE TYPE: peptide
SEQUENCE: 16

Ile Ser **Thr** Arg Val **Thr** Asn Asp Asn Pro Glu Cys Arg Leu Val
Lys
1 5 10 15
Glu **Thr** Arg Ile Cys Glu Val Arg Pro Cys
20 25

SEQUENCE CHARACTERISTICS:
LENGTH: 21 amino acids
TYPE: amino acid
STRANDEDNESS: not relevant
TOPOLOGY: not relevant
MOLECULE TYPE: peptide
SEQUENCE: 17

Lys Tyr Cys Gly Ser Cys Val Asp Gly Arg Cys Cys **Thr** Pro Leu Gln
1 5 10 15
Thr Arg **Thr** Val Lys
20

L12 ANSWER 4 OF 63 USPATFULL

ACCESSION NUMBER: 2002:88222 USPATFULL
TITLE: Methods to diagnose a required regulation of trophoblast invasion
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APPLICATION INFO.:	US 1999-380662		19991221	(9)
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SUMM During placental development the establishment of fetal-maternal interactions is critical for a successful human pregnancy (1). Abnormalities of **placenta** formation due to shallow trophoblast invasion have been linked to preeclampsia and fetal growth restriction (2). In contrast, uncontrolled trophoblast invasion and abnormal trophoblast growth are associated with hydatiform mole and choriocarcinoma. In the course of **placenta** formation, chorionic villous cytotrophoblasts undergo two morphologically distinct pathways of differentiation. The vast majority of cytotrophoblasts in both floating and. . .

SUMM . . . and preterm delivery. There is currently no effective pharmacologic treatment for preeclampsia and the only remedy is to remove the **placenta** (and hence deliver the fetus preterm). Current protocols, including bedrest and antihypertensive drugs, seek to stabilize maternal/fetal condition until delivery. . .

SUMM The present inventors have studied the mechanisms that regulate trophoblast invasion. The inventors have found that **antisense** disruption of the expression of the TGF.beta. receptor, endoglin, triggers invasion of cytotrophoblast from first trimester villous explants in vitro. . . role for TGF-.beta..sub.3 as an endogenous inhibitor of trophoblast invasion. Down-regulation of TGF-.beta..sub.3 (but not .beta..sub.1 or .beta..sub.2) expression using **antisense** oligonucleotides, stimulated extravillous trophoblast cell (EVT) outgrowth/migration and fibronectin production in 5-8 villous explants indicating that TGF-.beta..sub.3 acts to suppress in vivo trophoblast invasion. The effects of **antisense** treatment to TGF-.beta..sub.3 are specific as they are prevented by addition of exogenous TGF-.beta..sub.3 but not TGF-.beta..sub.1 or TGF-.beta..sub.2. The. . .

SUMM . . . the finding that TGF-.beta..sub.3 is highly expressed in trophoblast tissue of preeclamptic patients when compared to that in age-matched control **placenta** while there was no change in the expression of either the .beta..sub.1 or .beta..sub.2 isoform. Fibronectin and .alpha..sub.5 integrin expression were also greater in preeclamptic **placenta**, indicating that in preeclampsia, where there is shallow trophoblast invasion, trophoblast cells are arrested as an .alpha..sub.5 integrin phenotype producing TGF-.beta..sub.3. These data are supported by the finding that villous explants from a control (non-preeclamptic **placenta**, 32 weeks of gestation) spontaneously formed columns of trophoblasts that invaded the surrounding Matrigel, while explants from a preeclamptic **placenta** did not.

SUMM . . . been found to trigger trophoblast invasion. Follistatin an activin binding protein, inhibited the stimulatory effect of activin, and antibodies and **antisense** to endoglin.

SUMM . . . TGF.beta., but via R-I and R-II they come under the control of this ligand upon entering the decidua. In addition, **antisense** induced disruption of RI (ALK-1) and RII expression stimulated trophoblast outgrowth/migration and fibronectin synthesis. In contrast, **antisense** to RI (ALK-5) inhibited fibronectin synthesis.

DRWD FIG. 3A are Southern blots showing expression of TGF-.beta. isoforms in human **placenta** in the first trimester of gestation:

DRWD FIG. 4A are photographs showing that addition of recombinant TGF.beta..sub.3 to **antisense** TGF.beta..sub.3 abolishes the **antisense** stimulatory effect on trophoblast budding and outgrowth;

DRWD FIG. 4B are blots showing the reversal effect on **antisense** TGF.beta..sub.3 stimulatory effect by exogenous TGF.beta..sub.3 for fibronectin synthesis;

DRWD FIG. 4D are blots showing the effects on gelatinase activity in conditioned media of explants treated with sense or **antisense** oligonucleotides to TGF.beta..sub.3;

DRWD FIG. 4E are blots showing that the **antisense** TGF.beta..sub.3

stimulatory effect on fibronectin production is lost after 9 weeks of gestation:

DRWD FIG. 6A are photographs showing that **antisense** oligonucleotides to TGF.beta..sub.3 induces the formation of trophoblast cells in preeclamptic villous explants;

DRWD FIG. 6B shows the results of gelatin Zymography of explants of 32 weeks gestation from preeclamptic placentae treated with **antisense** or control sense oligonucleotides to TGF.beta..sub.3 for 5 days;

DRWD FIG. 6C are Western blots with MMP9 antisera of explants of 32 weeks gestation from preeclamptic placentae treated with **antisense** or control sense oligonucleotides to TGF.beta..sub.3 for 5 days;

DRWD FIG. 7A is a blot showing expression of HIF-1.alpha. **placenta** in the first trimester of gestation;

DRWD FIG. 7B is a blot showing expression of HIF-1.alpha. in preeclamptic (PE) and age-matched control **placenta** (C);

DRWD FIG. 10 are photographs showing the effect of **antisense** to HIF-1.alpha. on villous explant morphology.

DETD . . . R-II, or RI-RII-endoglin complex) or fragments thereof, may be inverted relative to its normal presentation for transcription to produce an **antisense** nucleic acid molecule. An **antisense** nucleic acid molecule may be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. Examples of **antisense** molecules for TGF.beta..sub.3 are 5'-CCTTTGCAAGTGCATC-3' (SEQ ID NO:1) and 5'-GATGCACTTGCAAAGG-3' (SEQ ID NO:2).

DETD . . . using physical techniques such as microinjection and electroporation or chemical methods such as coprecipitation and incorporation of DNA into liposomes. **Antisense** molecules may also be introduced in vivo using these conventional methods.

DETD Villous explants kept in culture for 6 days in the presence or absence of **antisense** oligonucleotides to endoglin were dissected away from the insert membrane with the supporting Matrigel. Explants and placental tissue of 9. . .

DETD **Antisense** Oligonucleotides and Their Effects on EVT Formation

DETD . . . against sequences adjacent to the AUG initiation codon of human endoglin (23) mRNA were synthesized. Previous studies have demonstrated that **antisense** oligonucleotides, targeted to sequences adjacent to initiation codons, are most efficient in inhibiting translation (24). Furthermore, 16-mer oligonucleotides are short. . . be taken up efficiently and provide sufficient specificity for hybridization to the corresponding target mRNA (24). The sequences of the **antisense** and sense endoglin oligonucleotides were 5'-GCGTGCCGCGGTCCAT-3' (SEQ ID NO:3) and 5'-ATGGACCGCGGCACGC-3' (SEQ ID NO:4), respectively. An oligomer with the same composition as the **antisense** oligonucleotide, but with a scrambled sequence, 5'-GCGGGCCTCGTTCCAG-3' (SEQ ID NO:5), was also synthesized and used as a negative control. Oligonucleotides were dissolved in water and their concentration was estimated by optical density at OD.sub.260. **Antisense** or sense oligonucleotides (5-10 .mu.M) were added to the villous explants on day 1 and day 3 of culture. EVT. . .

DETD . . . DMEM/F12. Explants were then washed and incubated in DMEM/F12 containing either 10 .mu.g/ml MAb 44G4 or non-immune IgG, 10 .mu.M **antisense**, scrambled or sense endoglin oligonucleotides. The medium with or without the various agents was changed on day 3 and was. . .

DETD Villous explants of 5-8 weeks gestation, cultured for 48 h with and without **antisense** ON to endoglin, were incubated in the presence of 1 .mu.Ci of [.sup.3H]thymidine per milliliter of medium. After 6 h. . .

DETD Stimulation of EVT Outgrowth and Migration by Antibody and **Antisense** Oligonucleotides to Endoglin

DETD **Antisense** endoglin also enhanced the number of EVT outgrowths as well as their migration and invasion into the Matrigel. Control explants,. . .

DETD The stimulatory effect of **antisense** endoglin oligonucleotides on EVT outgrowth and migration was observed on day 3 of culture with 6.87.+-.1.5 in the **antisense**-treated group versus 1.42.+-.0.41 in the sense-treated group ($p<0.05$). After 5 days of exposure, the number of EVT/villous tip increased from 2.08.+-.0.47 in sense-treated explants to 8.46.+-.1.7 in **antisense**-treated cultures. The **antisense**-endoglin effect on trophoblast differentiation was specific as incubation of explants with an equivalent amount of either sense endoglin or scrambled **antisense**-endoglin oligonucleotide (not shown) had no effect. **Antisense** endoglin stimulated EVT outgrowth and migration in a concentration-dependent manner with maximal stimulation observed at 10 .mu.M.

DETD . . . undergo proliferation (21), whereas differentiated EVT do not. Therefore, studies were carried out to determine if EVT outgrowth triggered by **antisense** endoglin treatment was due to cell division or migration. [.sup.3H]Thymidine autoradiography of explants exposed to **antisense** endoglin ON showed villous trophoblast proliferation within the villous tip at the proximal site of the forming column, while both. . .

DETD . . . repertoire (4). When placental explants of 5-8 weeks gestation were maintained in culture for 5 days in the presence of **antisense**-endoglin oligonucleotides, the stimulation of EVT outgrowth and migration was also accompanied by changes in integrin expression. The .alpha..sub.6 integrin subunit. . .

DETD . . . EVT outgrowth is observed under basal culture conditions, the expression of endoglin in trophoblast columns could only be studied in **antisense**-treated explants. Immunohistochemical analysis of explants treated with **antisense** oligonucleotides to endoglin revealed that in intact villi the syncytiophoblast maintained high levels of endoglin. Low levels of endoglin and. . . appears non-specific as it was also observed with non-immune IgG. The staining of endoglin in EVT of explants treated with **antisense** endoglin was weakly positive when compared to sections of the same explant stained with control IgG. In addition, endoglin expression in proximal columns of explants was much reduced when compared to sections of 9 weeks gestation **placenta** stained under similar conditions. When a subsequent section of this **placenta** is stained for .alpha..sub.5 integrin, the transition zone in the proximal column is clearly visualized as negative for .alpha..sub.5, but positive for endoglin. The .alpha..sub.5 integrin in explants treated with **antisense** endoglin was also found to be highly expressed in EVT within proximal and distal columns. These data suggest that **antisense** endoglin treatment, which promotes EVT outgrowth and migration in explant cultures, induces a decrease in endoglin expression at the level. . .

DETD . . . the anchoring villi and its production is increased during EVT differentiation (27). Thus the effect of either 44G4 IgG or **antisense** endoglin on fibronectin synthesis by villous explants from 5-8 weeks gestation was investigated. Explants were metabolically labelled on day 4. . . and newly synthesized FN released into the media over a period of 18 h was measured. Both 44G4 IgG and **antisense**-endoglin oligonucleotides induced a significantly greater production of FN than that observed in control IgG or sense oligonucleotide-treated cultures. PhosphoImager analysis. . . a 8- and 5-fold increase in FN synthesis (5 independent experiments carried out in triplicate, $p<0.05$) for 44G4 IgG and **antisense**-endoglin treated explants, respectively, relative to control sense or DMEM/F12 alone. FN production in villous explants, cultured in the presence of a scrambled **antisense** endoglin oligonucleotide, was similar to that observed in sense-treated explants or in medium alone.

DETD . . . essential component of the receptor complex in mediating the effects of TGF-.beta..sub.1 and TGF-.beta..sub.3, villous explants were preincubated with either **antisense** or antibody to endoglin to trigger EVT differentiation. After an overnight incubation, exogenous

TGF-.beta..sub.1, TGF-.beta..sub.2 or TGF-.beta..sub.3 were added at. . . were metabolically labelled at day 5 of culture and FN synthesis was measured. PhosphoImager analysis demonstrated that both antibody and **antisense** to endoglin significantly stimulated FN synthesis. Addition of exogenous TGF-.beta..sub.1 and TGF-.beta..sub.3 to explant cultures incubated with **antisense** ON or antibody to endoglin, which binds both isoforms, did not alter the stimulatory effect of **antisense** ON and antibody to endoglin on FN synthesis. In contrast, addition of TGF-.beta..sub.2, which does not interact with endoglin, overcame the antibody and **antisense** ON stimulatory effect on FN synthesis. TGF-.beta..sub.2, but not -.beta..sub.1 and -.beta..sub.3, inhibited also the EVT outgrowth and migration induced by the **antisense** endoglin treatment.

DETD Treatment of human villous explants from 5-8 weeks gestation with antibodies and **antisense** oligonucleotides to endoglin stimulated EVT differentiation along the invasive pathway. This was manifested by 1) a significant increase in EVT. . .

DETD . . . endoglin may contribute to the major complications of pregnancy such as preeclampsia or choriocarcinoma, associated with abnormal trophoblast invasion and **placenta** development.

DETD . . . with an upregulation of fibronectin synthesis and integrin switching. Trophoblast invasion at 5-7 weeks can be induced by incubation with **antisense** to TGF-.beta..sub.3, TGF.beta. receptor I (ALK-1) or TGF.beta. receptor II. Only minimal invasion occurred in response to **antisense** to TGF.beta..sub.1 and **antisense** TGF.beta..sub.2 failed to induce invasion. These data suggest that TGF-.beta..sub.3 via the ALK-1-receptor II complex is a major regulator of. . .

DETD Total RNA was extracted from the **placenta**, reverse transcribed and amplified by 15 cycles of PCR using TGF.beta. isoform specific primers. RT-PCR products were analysed by Southern. . .

DETD Villous explant cultures were established as described previously (I. Caniggia et al. Endocrinology, 138, 3976 1997, O. Genbacev et al., **Placenta** 13:439, 1992) from first trimester human placentae (5-10 weeks gestation) or from preeclamptic and age-matched control placentae (30 and 32. . . (L. Chesley, Obstet. Gynecol. 65, 423, 1985). Following an overnight period in serum-free DMEM/F12, explants were cultured in media containing **antisense** or sense oligonucleotides (10 .mu.M) for up to 6 days (with changes of media/oligonucleotides every 48 hours). Phosphorothioate oligonucleotides of. . .

DETD . . . W. K. Ritchie, S. J. Lye, M. Letarte, Endocrinology, 138, 4977 (1997), O. Genbacev, S. A. Schubach, R. K. Miller, **Placenta** 13, 439, (1992)). Morphologic (EVT outgrowth) and biochemical (fibronectin [FN] synthesis and gelatinase activity) indices of trophoblast invasion were monitored in response to **antisense** (AS) induced suppression of TGF.beta. isoform expression in explants at 5-8 weeks of gestation. Explants exposed to AS TGF.beta..sub.3 (but. . .

DETD . . . .alpha..sub.5 and fail to express .alpha..sub.1 were also obverved in preeclamptic placentae. These data suggest that the trophoblasts from preeclamptic **placenta** are arrested at a relatively immature phenotype possibly due to a failure to undergo complete differentiation along the invasive pathway. . .

DETD . . . here demonstrate not only that abnormalities in TGF.beta..sub.3 expression are associated with preeclampsia but also that down-regulation of TGF.beta..sub.3 with **antisense** oligonucleotides restores the invasive capability of preeclamptic trophoblasts. The data are consistent with a model of normal placentation in which. . . contributes to the remodelling of the uterine spiral arteries and ultimately enables the establishment of increased vascular perfusion of the **placenta**. In placentae predisposed to preeclampsia, TGF.beta..sub.3 expression remains abnormally elevated and trophoblasts remain in a relatively immature

state of differentiation.. . .

DETD . . . FIG. 9 showing the effect of low oxygen tension on villous explant morphology; and FIG. 10 showing the effect of **antisense** to HIF-1.alpha. on villous explant morphology.

DETD . . . TGF.beta..sub.3, R-I is expressed at greater levels in trophoblast tissue of preeclamptic patients when compared to that in age-matched control **placenta**. **Antisense** disruption of R-I (ALK-1) and R-II expression stimulated trophoblast outgrowth/migration and FN synthesis. In contrast, **antisense** to R-I (ALK-5) inhibited FN synthesis.

DETD 1. Cross J C, Werb Z, Fisher, S J, 1994. **Implantation** and the **placenta**: key pieces of the development puzzle. Science, 266:1508-1518.

DETD 3. Aplin J D, 1991. **Implantation**, trophoblast differentiation and haemochorial placentation: mechanistic evidence in vivo and in vitro. J. Cell Science, 99: 681-692.

DETD . . . Lye S J, Letarte M, 1994. Localization of endoglin, a transforming growth-factor-b binding protein, and of CD44 and integrins in **placenta** during the first trimester of pregnancy. Biol Reprod. 51: 405-413.

DETD . . . J A, Lala P K, 1995. Localization of transforming growth factor b and its natural inhibitor decorin in the human **placenta** and decidua throughout gestation. **Placenta**, 16: 221-231.

DETD . . . I and type II transforming growth factor-b (TGF-b) receptors with different affinities for TGF-b1 and TGF-b2 are exhibited by human **placenta** trophoblasts. J. Cell. Physiol. 150: 334-343.

DETD 21. Genbacev O, Schubach S A, Miller R K, (1992). Villous culture of first trimester human **placenta**-Model to study extravillous trophoblast (EVT) differentiation. **Placenta**, 13: 439-461.

DETD 24. Malcolm A D B, 1992. Uses and applications of **antisense** oligonucleotides: uses of **antisense** nucleic acids-an introduction. Bioch. Soc. Trans. 20: 745-746.

DETD 27. Feinberg R F, Kilman H J, Locwood C J, 1991 Is oncofetal fibronectin a trophoblast glue for human **implantation**? Am. J. Pathol. 138: 537-543.

DETD . . . C J, Aplin J D, 1995. Trophoblast differentiation during formation of anchoring villi in a model of the early human **placenta** in vitro. **Placenta**, 16: 41-56.

DETD . . . F, Kliman H J, Wang C-L, 1994. Transforming growth factor-b stimulates trophoblast oncofetal fibronectin synthesis in vitro: implications for trophoblast **implantation** in vivo. J.Clin. Endocrinol Metab. 78: 1241-1248.

DETD Expression of TGF-.beta. isoforms in human **placenta** in the first trimester of gestation. (FIG. 3A) Message expression of TGF.beta. isoforms was assessed by low cycle RT-PCR followed. . . column (EVT, thin arrow) but was absent in the transitional zone where polarized cells become unpolarized (thick arrows). Sections of **placenta** at 12 weeks gestation demonstrate low or absent TGF-.beta..sub.3 immunoreactivity in the villi. There is no immunoreactivity when antiserum was. . .

DETD **Antisense** TGF.beta..sub.3 stimulates trophoblast migration, fibronectin production and gelatinase, activity. Explants of 5-8 weeks gestation were treated for 5 days with 10 .mu.M **antisense** oligonucleotides to TGF.beta..sub.3 (AS-.beta.3), AS-.beta.3 plus 10 ng/ml recombinant TGF.beta..sub.3 (AS-.beta.3+.beta.3) or AS-.beta.3 plus recombinant TGF.beta.1 (AS-.beta.3+.beta.1). Control experiments were. . . (S-.beta.3) or medium alone (FIG. 4C). (FIG. 4A) Shown is a representative experiment demonstrating that addition of recombinant TGF.beta..sub.3 to **antisense** TGF.beta..sub.3 treated explants (AS-.beta.3+.beta.3) abolishes the **antisense** stimulatory effect on trophoblasts budding and outgrowth (arrows). (FIG. 4B) Similar reversal effect on AS-.beta.3 stimulatory effect by exogenous TGF.beta..sub.3. . . 4-6. AS-.beta.3 treated explants; lanes 7-9, AS-.beta.3+.beta.3 treated explants. (FIG. 4C) Changes in fibronectin

estimated after normalization to control cultures. **Antisense** TGF.beta..sub.3 treatment (AS-.beta.3, solid bar) significantly incresed ($p<0.05$; one-way ANOVA followed by Student-Newman-Keuls test for non-paired groups) the amount of. . . sense (S-.beta.3, cross bar). Addition of exogenous TGF.beta..sub.3 (AS-.beta.3+.beta.3 squares bar) but not TGF.beta..sub.1 (AS-.beta.3+.beta.1 cross hatched bar) to the **antisense** treated explants abolished the **antisense** stimulatory effect on fibronectin production, demonstrating the specificity of the action of TGF.beta..sub.3. (FIG. 4D) Getatinase activity in conditioned media of explants treated with sense or **antisense** oligonucleotides to TGF.beta.3. Arrows indicate positions of getatinases activity (MMP2: 60, 68; MMP9: 84 and 92, kDa). (FIG. 4E) The **antisense** TGF.beta..sub.3 stimulatory effect on fibronectin production is lost after 9 weeks of gestation. Explants of 6 and 10 weeks gestation were treated with 10 .mu.M **antisense** (AS-.beta.3) or control sense (S-.beta.3) oligonucleotides to TGF.beta..sub.3. Newly synthesized fibronectin was isolated from the medium as described above. Representative. . .

DETD **Antisense** oligonucleotides to TGF.beta..sub.3 induces the formation of columns of trophoblast cells in preeclamptic villous explants. Villous explant cultures were prepared from preeclamnptic and age-matched control placentae. Explants were maintained in culture in the presence of either control sense or **antisense** oligonucleotides to TGF.beta..sub.3 for 5 days. Morphological integrity was recoded daily. Explants from normal **placenta** (32 weeks), exposed to sense oligonucleotides (S-.beta.3) spontaneously form columns of trophoblast cells which migrate and invade into the surrounding Matrigel (arrows), while explants from preeclamptic **placenta** (32 weeks) exposed to sense oligonucleotides do not. In contrast, **antisense** treatment (AS-.beta.3) triggers the formation of invading trophoblast columns (arrows) in preeclamptic placentae.

DETD **Antisense** oligonucleotides to TGF.beta..sub.3 triggers gelatinase activity and expression in preeclamptic villous explants. Explants of 32 weeks gestation from preeclamptic placentae were treated with **antisense** (AS-.beta.3) or control sense (S-.beta.3) oligonucleotides to TGF.beta..sub.3 for 5 days. Samples of conditioned medium were collected at day 5. . .

```
DETD    . . .  ctg aac ttt gcc acg gtc agc ctc tct ctg tcc act tgc acc
        337
Ala Leu Leu Asn Phe Ala Thr Val Ser Leu Ser Leu Ser Thr Cys
        Thr
         15                  20                  25
acc ttg gac ttc ggc cac atc aag aag aag agg gtg gaa gcc att agg      385
  Thr Leu Asp Phe Gly His Ile Lys Lys Lys Arg Val Glu Ala Ile Arg
    30                  35                  40
gga cag atc.  .  .  aag ctc agg ctc acc agc ccc cct gag cca acg      433
Gly Gln Ile Leu Ser Lys Leu Arg Leu Thr Ser Pro Pro Glu Pro
        Thr
45                  50                  55                  60
gtg atg acc cac gtc ccc tat cag gtc ctg gcc ctt tac aac agc acc      481
Val Met Thr His Val Pro Tyr Gln Val Leu Ala Leu Tyr Asn Ser
        Thr
                65                  70                  75
cgg gag ctg ctg gag gag atg cat ggg gag agg gag gaa ggc tgc acc      529
Arg Glu Leu Leu Glu Glu Met His Gly Glu Arg Glu Glu Gly Cys Thr
            80                  85                  90
cag gaa aac acc gag tcg gaa tac tat gcc aaa gaa atc cat aaa ttc      577
Gln Glu Asn Thr Glu Ser Glu Tyr Tyr Ala Lys Glu Ile His Lys Phe
        95                  100                 105
gac atg atc cag ggg ctg.  .  .  115                 120
aaa gga att acc tcc aag gtt ttc cgc ttc aat gtg tcc tca gtg gag      673
Lys Gly Ile Thr Ser Lys Val Phe Arg Phe Asn Val Ser Ser Val Glu
125                 130                 135                 140
aaa aat aga acc aac cta ttc cga gca gaa ttc cgg gtc ttg cgg gtg      721
```

```
Lys Asn Arg Thr Asn Leu Phe Arg Ala Glu Phe Arg Val Leu Arg Val
                  145                 150                 155
ccc aac ccc agc tct aag.  .  .  185
aag aat ctg ccc aca cgg ggc act gcc gag tgg ctg tcc ttt gat gtc      865
Lys Asn Leu Pro Thr Arg Gly Thr Ala Glu Trp Leu Ser Phe Asp
       Val
    190                 195                 200
act gac act gtg cgt gag tgg ctg ttg aga aga gag tcc aac tta ggt      913
  Thr Asp Thr Val Arg Glu Trp Leu Leu Arg Arg Glu Ser Asn Leu
       Gly
205                 210                 215                 220
cta gaa atc agc att.  .  .  tgt cca tgt cac acc ttt cag ccc aat gga      961
Leu Glu Ile Ser Ile His Cys Pro Cys His Thr Phe Gln Pro Asn Gly
                  225                 230                 235
gat atc ctg gaa aac att cac gag gtg atg gaa atc aaa.  .  .  295
       300
gct ttg gac acc aat tac tgc ttc cgc aac ttg gag gag aac tgc tgt     1201
Ala Leu Asp Thr Asn Tyr Cys Phe Arg Asn Leu Glu Glu Asn Cys Cys
                  305                 310                 315
gtg cgc ccc ctc tac att.  .  .  cgc agt gca gac aca acc cac agc acg gtg ctg gga
       ctg     1345
Pro Tyr Leu Arg Ser Ala Asp Thr Thr His Ser Thr
       Val Leu Gly Leu
    350                 355                 360
tac aac act ctg aac cct gaa gca tct gcc tcg cct tgc tgc gtg ccc     1393
Tyr Asn Thr Leu Asn Pro Glu Ala Ser Ala Ser Pro Cys Cys Val Pro
365                 370                 375                 380
cag gac ctg gag ccc ctg acc atc ctg tac tat gtt ggg agg acc ccc     1441
Gln Asp Leu Glu Pro Leu Thr Ile Leu Tyr Tyr Val Gly Arg Thr
       Pro
                  385                 390                 395
aaa gtg gag cag ctc tcc aac atg gtg gtg aag tct tgt aaa tgt agc     1489
Lys.  .  .  21
Met Lys Met His Leu Gln Arg Ala Leu Val Val Leu Ala Leu Leu Asn
1                 5                   10                  15
Phe Ala Thr Val Ser Leu Ser Leu Ser Thr Cys Thr
       Thr Leu Asp Phe
                  20                  25                  30
Gly His Ile Lys Lys Lys Arg Val Glu Ala Ile Arg Gly Gln Ile Leu
        35                  40                  45
Ser Lys Leu Arg Leu Thr Ser Pro Pro Glu Pro Thr Val Met
       Thr His
    50                  55                  60
Val Pro Tyr Gln Val Leu Ala Leu Tyr Asn Ser Thr Arg Glu Leu Leu
65                  70                  75                  80
Glu Glu Met His Gly Glu Arg Glu Glu Gly Cys Thr Gln Glu Asn
       Thr
                  85                  90                  95
Glu Ser Glu Tyr Tyr Ala Lys Glu Ile His Lys Phe Asp Met Ile Gln
             100                 105                 110
Gly Leu Ala Glu His Asn Glu Leu Ala Val Cys Pro Lys Gly Ile Thr
        115                 120                 125
Ser Lys Val Phe Arg Phe Asn Val Ser Ser Val Glu Lys Asn Arg Thr
    130                 135                 140
Asn Leu Phe Arg Ala Glu Phe Arg Val Leu Arg Val Pro Asn Pro Ser
145                 150                 155.  .  .  165                 170
       175
Asp Glu His Ile Ala Lys Gln Arg Tyr Ile Gly Gly Lys Asn Leu Pro
             180                 185                 190
  Thr Arg Gly Thr Ala Glu Trp Leu Ser Phe Asp Val Thr
       Asp Thr Val
        195                 200                 205
Arg Glu Trp Leu Leu Arg Arg Glu Ser Asn Leu Gly Leu Glu Ile Ser
    210                 215                 220
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Ile His Cys Pro Cys His Thr Phe Gln Pro Asn Gly Asp Ile Leu Glu
225                 230                 235                 240
Asn Ile His Glu Val Met Glu Ile Lys.  .  .  His Arg Leu
        275                 280                 285
Asp Asn Pro Gly Gln Gly Gly Gln Arg Lys Lys Arg Ala Leu Asp Thr
    290                 295                 300
Asn Tyr Cys Phe Arg Asn Leu Glu Glu Asn Cys Cys Val Arg Pro Leu
305                 310                 315.  .  .  Gly Tyr Tyr Ala Asn Phe Cys
       Ser Gly Pro Cys Pro Tyr Leu Arg
            340                 345                 350
Ser Ala Asp Thr Thr His Ser Thr Val Leu Gly Leu
       Tyr Asn Thr Leu
        355                 360                 365
Asn Pro Glu Ala Ser Ala Ser Pro Cys Cys Val Pro Gln Asp Leu Glu
    370                 375                 380
Pro Leu Thr Ile Leu Tyr Tyr Val Gly Arg Thr Pro Lys Val Glu
       Gln
385                 390                 395                 400
Leu Ser Asn Met Val Val Lys Ser Cys Lys Cys Ser
                405.  .  .  gtg atg agg ctt acc atc agc tat ttg cgt gtg agg aaa
       ctt      244
Ala Ser Val Met Arg Leu Thr Ile Ser Tyr Leu Arg Val Arg Lys Leu
            60                  65                  70
ctg gat gct ggt gat ttg gat att gaa.  .  .  gtt atg gtt ctc aca      340
Asn Cys Phe Tyr Leu Lys Ala Leu Asp Gly Phe Val Met Val Leu Thr
    90                  95                  100
gat gat ggt gac atg att tac att tct gat aat gtg aac aaa tac atg      388
Asp Asp.  .  .  110                 115                 120
gga tta act cag ttt gaa cta act gga cac agt gtg ttt gat ttt act      436
Gly Leu Thr Gln Phe Glu Leu Thr Gly His Ser Val Phe Asp Phe
       Thr
                125                 130                 135
cat cca tgt gac cat gag gaa atg aga gaa atg ctt aca cac aga aat      484
His Pro Cys Asp His Glu Glu Met Arg Glu Met Leu Thr His Arg Asn
            140                 145                 150
ggc ctt gtg aaa aag ggt aaa gaa caa aac aca cag cga agc ttt ttt      532
Gly Leu Val Lys Lys Gly Lys Glu Gln Asn Thr Gln Arg Ser Phe Phe
        155                 160                 165
ctc aga atg aag tgt acc cta act agc cga gga aga act atg aac ata      580
Leu Arg Met Lys Cys Thr Leu Thr Ser Arg Gly Arg Thr
       Met Asn Ile
    170                 175                 180
aag tct gca aca tgg aag gta ttg cac tgc aca ggc cac att cac gta      628
Lys Ser Ala Thr Trp Lys Val Leu His Cys Thr Gly His Ile His
       Val
185                 190                 195                 200
tat gat acc aac agt aac caa cct cag tgt ggg tat aag aaa cca cct      676
Tyr Asp Thr Asn Ser Asn Gln Pro Gln Cys Gly Tyr Lys Lys Pro Pro
                205                 210                 215
atg acc tgc ttg gtg ctg att tgt gaa ccc att cct cac cca tca aat      724
Met Thr Cys Leu Val Leu Ile Cys Glu Pro Ile Pro His Pro Ser Asn
            220                 225                 230
att gaa att cct.  .  .  tta gat agc aag act ttc ctc agt cga cac agc ctg
       772
Ile Glu Ile Pro Leu Asp Ser Lys Thr Phe Leu Ser Arg His Ser Leu
        235                 240                 245
gat atg aaa ttt tct tat tgt gat gaa aga att acc gaa ttg atg gga      820
Asp Met Lys Phe Ser Tyr Cys Asp Glu Arg Ile Thr Glu Leu Met Gly
    250                 255                 260
tat gag cca gaa gaa ctt tta ggc cgc tca att tat gaa tat.  .  .  tct gat cat ctg
       acc aaa act cat cat gat atg ttt act      916
Ala Leu Asp Ser Asp His Leu Thr Lys Thr His His Asp Met Phe
       Thr
                285                 290                 295
```

```
aaa gga caa gtc acc aca gga cag tac agg atg ctt gcc aaa aga ggt      964
Lys Gly Gln Val Thr Thr Gly Gln Tyr Arg Met Leu Ala Lys Arg
       Gly
             300                 305                 310
gga tat gtc tgg gtt gaa act caa gca act gtc ata tat aac acc aag     1012
Gly Tyr Val Trp Val Glu Thr Gln Ala Thr Val Ile Tyr Asn
       Thr Lys
         315                 320                 325
aat tct caa cca cag tgc att gta tgt gtg aat tac gtt gtg agt ggt     1060
Asn.  .  .  tcc ctt caa caa aca gaa tgt gtc     1108
Ile Ile Gln His Asp Leu Ile Phe Ser Leu Gln Gln Thr Glu Cys Val
345                 350                 355                 360
ctt aaa ccg gtt gaa tct tca gat atg aaa atg act cag cta ttc acc     1156
Leu Lys Pro Val Glu Ser Ser Asp Met Lys Met Thr Gln Leu Phe
       Thr
                365                 370                 375
aaa gtt gaa tca gaa gat aca agt agc ctc ttt gac aaa ctt aag aag     1204
Lys Val Glu Ser Glu Asp Thr Ser Ser Leu Phe Asp Lys Leu Lys Lys
             380                 385                 390
gaa cct gat gct tta act ttg ctg gcc cca gcc gct gga gac aca atc     1252
Glu Pro Asp Ala Leu Thr Leu Leu Ala Pro Ala Ala Gly Asp Thr
       Ile
         395                 400                 405
ata tct tta gat ttt ggc agc aac gac aca gaa act gat gac cag caa     1300
Ile Ser Leu Asp Phe Gly Ser Asn Asp Thr Glu Thr Asp Asp Gln
       Gln
    410                 415                 420
ctt gag gaa gta cca tta tat aat gat gta atg ctc ccc tca.  .  .  tct cca tta ccc
       acc gct     1396
Glu Lys Leu Gln Asn Ile Asn Leu Ala Met Ser Pro Leu Pro Thr Ala
                445                 450                 455
gaa acg cca aag cca ctt cga agt agt gct gac cct gca ctc aat caa     1444
Glu Thr Pro Lys Pro Leu Arg Ser Ser Ala Asp Pro Ala Leu Asn Gln
             460                 465                 470
gaa gtt gca tta.  .  .  Ser
         475                 480                 485
ttt acc atg ccc cag att cag gat cag aca cct agt cct tcc gat gga     1540
Phe Thr Met Pro Gln Ile Gln Asp Gln Thr Pro Ser Pro Ser Asp
       Gly
    490                 495                 500
agc act aga caa agt tca cct gag cct aat agt ccc agt gaa tat tgt     1588
Ser Thr Arg Gln Ser Ser Pro Glu Pro Asn Ser Pro Ser Glu Tyr Cys
505                 510                 515                 520
ttt tat gtg gat.  .  .  ttt gct gaa gac aca gaa gca aag aac cca ttt tct act
       1684
Glu Lys Leu Phe Ala Glu Asp Thr Glu Ala Lys Asn Pro Phe Ser
       Thr
             540                 545                 550
cag gac aca gat tta gac ttg gag atg tta gct ccc tat atc cca atg     1732
Gln Asp Thr Asp Leu Asp Leu Glu Met Leu Ala Pro Tyr Ile Pro Met
         555                 560                 565
gat gat gac ttc cag.  .  .  agt cct caa agc aca gtt aca     1828
Ser Ser Ser Ala Ser Pro Glu Ser Ala Ser Pro Gln Ser Thr Val
       Thr
585                 590                 595                 600
gta ttc cag cag act caa ata caa gaa cct act gct aat gcc acc act     1876
Val Phe Gln Gln Thr Gln Ile Gln Glu Pro Thr Ala Asn Ala
       Thr Thr
                605                 610                 615
acc act gcc acc act gat gaa tta aaa aca gtg aca aaa gac cgt atg     1924
  Thr Thr Ala Thr Thr Asp Glu Leu Lys
       Thr Val Thr Lys Asp Arg Met
             620                 625                 630
gaa gac att aaa ata ttg att gca tct cca tct cct acc cac ata cat     1972
```

```
Glu Asp Ile Lys Ile Leu Ile Ala Ser Pro Ser Pro Thr His Ile His
        635                 640                 645
aaa gaa act act agt gcc aca tca tca cca tat aga gat act caa agt     2020
Lys Glu Thr Thr Ser Ala Thr Ser Ser Pro Tyr Arg
      Asp Thr Gln Ser
    650                 655                 660
cgg aca gcc tca cca aac aga gca gga aaa gga gtc ata gaa cag aca     2068
Arg Thr Ala Ser Pro Asn Arg Ala Gly Lys Gly Val Ile Glu Gln
      Thr
665                 670                 675                 680
gaa aaa tct cat cca aga agc cct aac gtg tta tct gtc gct ttg agt     2116
Glu Lys.  .  . 685                 690                 695
caa aga act aca gtt cct gag gaa gaa cta aat cca aag ata cta gct     2164
Gln Arg Thr Thr Val Pro Glu Glu Glu Leu Asn Pro Lys Ile Leu
      Ala
            700                 705                 710
ttg cag aat gct cag aga.  .  . gta gga att gga aca tta tta cag cag cca gac gat
      cat    2260
Phe Gln Ala Val Gly Ile Gly Thr Leu Leu Gln Gln Pro Asp Asp His
    730                 735                 740
gca gct act aca tca ctt tct tgg aaa cgt gta aaa gga tgc aaa tct     2308
Ala Ala Thr Thr Ser Leu Ser Trp Lys Arg Val Lys Gly Cys Lys Ser
      Ser
745                 750                 755                 760
agt gaa cag aat gga atg gag caa aag aca att att tta ata ccc tct     2356
Ser Glu Gln Asn Gly Met Glu Gln Lys Thr Ile Ile Leu Ile Pro Ser
                765                 770                 775
gat tta gca tgt aga ctg ctg ggg caa tca atg gat.  .  . 785                 790
cca cag ctg acc agt tat gat tgt gaa gtt aat gct cct ata caa ggc     2452
Pro Gln Leu Thr Ser Tyr Asp Cys Glu Val Asn Ala Pro Ile Gln Gly
      795                 800                 805
agc aga aac cta ctg cag.  .  .
DETD  .  .  . Pro Leu Pro His
        35                  40                  45
Asn Val Ser Ser His Leu Asp Lys Ala Ser Val Met Arg Leu Thr Ile
    50                  55                  60
Ser Tyr Leu Arg Val Arg Lys Leu Leu Asp Ala Gly Asp Leu Asp Ile
65                  70.  .  . Ala Gln Met Asn Cys Phe Tyr Leu Lys Ala Leu
                85                  90                  95
Asp Gly Phe Val Met Val Leu Thr Asp Asp Gly Asp Met Ile Tyr Ile
            100                 105                 110
Ser Asp Asn Val Asn Lys Tyr Met Gly Leu Thr Gln Phe Glu Leu
      Thr
        115                 120                 125
Gly His Ser Val Phe Asp Phe Thr His Pro Cys Asp His Glu Glu Met
    130                 135                 140
Arg Glu Met Leu Thr His Arg Asn Gly Leu Val Lys Lys Gly Lys Glu
145                 150                 155                 160
Gln Asn Thr Gln Arg Ser Phe Phe Leu Arg Met Lys Cys Thr Leu
      Thr
                165                 170                 175
Ser Arg Gly Arg Thr Met Asn Ile Lys Ser Ala Thr Trp Lys Val
      Leu
            180                 185                 190
His Cys Thr Gly His Ile His Val Tyr Asp Thr Asn Ser Asn Gln
      Pro
        195                 200                 205
Gln Cys Gly Tyr Lys Lys Pro Pro Met Thr Cys Leu Val Leu Ile Cys
    210                 215                 220
Glu Pro Ile Pro His Pro Ser Asn Ile Glu Ile Pro Leu Asp Ser Lys
225                 230                 235                 240
  Thr Phe Leu Ser Arg His Ser Leu Asp Met Lys Phe Ser Tyr Cys Asp
                245                 250                 255
Glu Arg Ile Thr Glu Leu Met Gly Tyr Glu Pro Glu Glu Leu Leu Gly
```

260 265 270
Arg Ser Ile Tyr Glu Tyr Tyr His Ala Leu Asp Ser Asp His Leu **Thr**
275 280 285
Lys **Thr** His His Asp Met Phe **Thr** Lys Gly Gln Val **Thr**
Thr Gly Gln
290 295 300
Tyr Arg Met Leu Ala Lys Arg Gly Gly Tyr Val Trp Val Glu **Thr** Gln
305 310 315 320
Ala **Thr** Val Ile Tyr Asn **Thr** Lys Asn Ser Gln Pro Gln Cys Ile
Val
325 330 335
Cys Val Asn Tyr Val Val Ser Gly Ile Ile Gln His Asp Leu Ile Phe
340 345 350
Ser Leu Gln Gln **Thr** Glu Cys Val Leu Lys Pro Val Glu Ser Ser Asp
355 360 365
Met Lys Met **Thr** Gln Leu Phe **Thr** Lys Val Glu Ser Glu Asp
Thr Ser
370 375 380
Ser Leu Phe Asp Lys Leu Lys Lys Glu Pro Asp Ala Leu **Thr** Leu Leu
385 390 395 400
Ala Pro Ala Ala Gly Asp **Thr** Ile Ile Ser Leu Asp Phe Gly Ser Asn
405 410 415
Asp **Thr** Glu **Thr** Asp Asp Gln Gln Leu Glu Glu Val Pro Leu Tyr
Asn
420 425 430
Asp Val Met Leu Pro Ser Pro Asn Glu Lys Leu Gln Asn Ile Asn Leu
435 440 445
Ala Met Ser Pro Leu Pro **Thr** Ala Glu **Thr** Pro Lys Pro Leu Arg
Ser
450 455 460
Ser Ala Asp Pro Ala Leu Asn Gln Glu Val Ala Leu Lys Leu Glu Pro
465 470 475 480
Asn Pro Glu Ser Leu Glu Leu Ser Phe **Thr** Met Pro Gln Ile Gln Asp
485 490 495
Gln **Thr** Pro Ser Pro Ser Asp Gly Ser **Thr** Arg Gln Ser Ser Pro
Glu
500 505 510
Pro Asn Ser Pro Ser Glu Tyr Cys Phe Tyr Val Asp. . . Asp Met Val
515 520 525
Asn Glu Phe Lys Leu Glu Leu Val Glu Lys Leu Phe Ala Glu Asp **Thr**
530 535 540
Glu Ala Lys Asn Pro Phe Ser **Thr** Gln Asp **Thr** Asp Leu Asp Leu
Glu
545 550 555 560
Met Leu Ala Pro Tyr Ile Pro Met Asp Asp Asp Phe Gln. . . Leu Ser Pro Leu Glu
Ser Ser Ser Ala Ser Pro Glu Ser
580 585 590
Ala Ser Pro Gln Ser **Thr** Val **Thr** Val Phe Gln Gln **Thr**
Gln Ile Gln
595 600 605
Glu Pro **Thr** Ala Asn Ala **Thr** **Thr** **Thr**
Thr Ala **Thr** **Thr** Asp Glu Leu
610 615 620
Lys **Thr** Val **Thr** Lys Asp Arg Met Glu Asp Ile Lys Ile Leu Ile
Ala
625 630 635 640
Ser Pro Ser Pro **Thr** His Ile His Lys Glu **Thr** **Thr**
Ser Ala **Thr** Ser
645 650 655
Ser Pro Tyr Arg Asp **Thr** Gln Ser Arg **Thr** Ala Ser Pro Asn Arg
Ala
660 665 670
Gly Lys Gly Val Ile Glu Gln **Thr** Glu Lys Ser His Pro Arg Ser Pro
675 680 685

Asn Val Leu Ser Val Ala Leu Ser Gln Arg **Thr** **Thr** Val Pro Glu
Glu
690 695 700
Glu Leu Asn Pro Lys Ile Leu Ala Leu Gln Asn Ala Gln Arg Lys Arg
705 710 715 720
Lys Met Glu His Asp Gly Ser Leu Phe Gln Ala Val Gly Ile Gly **Thr**
725 730 735
Leu Leu Gln Gln Pro Asp Asp His Ala Ala **Thr** **Thr** Ser Leu Ser
Trp
740 745 750
Lys Arg Val Lys Gly Cys Lys Ser Ser Glu Gln Asn Gly Met Glu Gln
755 760 765
Lys **Thr** Ile Ile Leu Ile Pro Ser Asp Leu Ala Cys Arg Leu Leu Gly
770 775 780
Gln Ser Met Asp Glu Ser Gly Leu Pro Gln Leu **Thr** Ser Tyr Asp Cys
785 790 795 800
Glu Val Asn Ala Pro Ile Gln Gly Ser Arg Asn Leu Leu Gln. . .

L12 ANSWER 5 OF 63 USPATFULL
ACCESSION NUMBER: 2002:63687 USPATFULL
TITLE: Prognostic compositions for prostate cancer and methods of use thereof
INVENTOR(S): Tricoli, James V., 106 Clover Leaf La., North Wales, PA, United States 19454
Rondinelli, Rachel, 418 Candlewood Way, Harleysville, PA, United States 19438

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6361948	B1	20020326	
	WO 9909215		19990225	<--
APPLICATION INFO.:	US 2000-485549		20001109	(9)
	WO 1998-US16768		19980813	
			20001109	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-55285P	19970813 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Horlick, Kenneth R.
LEGAL REPRESENTATIVE: Dean Dorfman Herrell & Skillman
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 1789
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6361948 B1 20020326
WO 9909215 19990225 <--
SUMM A third type of target cell for transgene introduction is the embryonal stem cell (ES). ES cells are obtained from pre-**implantation** embryos cultured in vitro (Evans, M. J., et al., (1981) Nature 292, 154-156; Bradley, A., et al. (1984) Nature 309,. . .
DETD . . . cDNA, genomic DNA, RNA, and fragments thereof which may be single- or double-stranded. Thus, this invention provides oligonucleotides (sense or **antisense** strands of DNA or RNA) having sequences capable of hybridizing with at least one sequence of a nucleic acid molecule. . .
DETD . . . one embodiment, the nucleic acid molecules of the invention may be used to decrease expression of CLAR1. In this embodiment, **antisense** molecules are employed which are targeted to expression-controlling sequences of CLAR1-encoding genes. **Antisense** oligonucleotides may be designed to hybridize to the complementary sequence of nucleic acid, pre-mRNA or mature mRNA,

interfering with the. . . or variant form thereof), so that its expression is reduced or prevented altogether. In addition to the CLAR1 coding sequence, **antisense** techniques can be used to target the control sequences of the CLAR1 gene, e.g. the 5' flanking sequence of the CLAR1 coding sequence such as the translation start site. **Antisense** oligomers should be sufficient length to hybridize to the target nucleotide sequence and exert the desired effect, e.g. blocking translation. . . smaller oligomers are likely to be more efficiently taken up by cells in vivo such that a greater number of **antisense** oligomers may be delivered to the location of the target mRNA. Preferably, **antisense** oligomers should be at least 15 nucleotides long to achieve adequate specificity. Oligonucleotides for use in **antisense** technology are preferably between 15 to 30 nucleotides in length. The use of **antisense** molecules to decrease expression levels of a pre-determined gene is known in the art. The construction of **antisense** sequences and their use is described in Peyman and Ulman, Chemical Reviews, 90:543-584, (1990), Crooke, Ann. Rev. Pharmacol. Toxical., 32:329-376, (1992), and Zamecnik and Stephenson, P.N.A.S., 75:280-284, (1974). Examples of **antisense** sequences for the two spliced forms of CLAR1 (SEQ ID NO: 2 and SEQ ID NO: 3) include:

DETD . . . multiple organ northern blots (CLONTECH) that contain 2 .mu.g of poly(A+) RNA from adult pancreas, kidney, skeletal muscle, liver, lung, **placenta**, brain, heart, peripheral blood leukocyte, colon, small intestine, ovary, testis, prostate, thymus, spleen and fetal kidney, liver, lung and brain. . .

DETD . . . His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, **Thr**; V, Val; W, Trp and Y, Tyr.

DETD . . . 2

LENGTH: 276

TYPE: PRT

ORGANISM: Homo sapiens

SEQUENCE: 2

```
Met Ser Phe Glu Gly Gly Asp Gly Ala Gly Pro Ala Met Leu Ala Thr
 1               5                  10                  15
Gly Arg Ala Arg Met Ala Ser Gly Arg Pro Glu Glu Leu Trp Glu Ala
            20                  25                  30
Val Val Gly Ala Ala Glu Arg Phe Arg Ala Arg Thr Gly Thr Glu
        Leu
         35                  40                  45
Val Leu Leu Thr Ala Ala Pro Pro Pro Pro Pro Arg Pro Gly Pro Cys
    50                  55                  60
Ala Tyr Ala Ala His Gly. . . Ala Glu Ala Ala Arg Arg
65                  70                  75                  80
Cys Leu His Asp Ile Ala Leu Ala His Arg Ala Ala Thr Ala Ala Arg
                85                  90                  95
Leu Pro Ala Pro Pro Pro Ala Pro Gln Pro Pro Ser Pro Thr Pro Ser
            100                 105                 110
Pro Pro Arg Pro Thr Leu Ala Arg Glu Asp Asn Glu Glu Asp Glu Asp
        115                 120                 125
Glu Pro Thr Glu Thr Glu Thr Ser Gly Glu Gln Leu
       Gly Ile Ser Asp
    130                 135                 140
Asn Gly Gly Leu Phe Val Met Asp Glu Asp Ala Thr Leu Gln Asp Leu
145                 150                 155                 160
Pro Pro Phe Cys Glu Ser Asp Pro Glu Ser Thr Asp Asp Gly Ser Leu
                165                 170                 175
Ser Glu Glu Thr Pro Ala Gly Pro Pro Thr Cys Ser Val Pro Pro
       Ala
            180                 185                 190
Ser Ala Leu Pro Thr Gln Gln Tyr Ala Lys Ser Leu Pro Val Ser Val
        195                 200                 205
Pro Val Trp Gly Phe Lys Glu Lys Arg Thr Glu Ala Arg Ser Ser Asp
```

210 215 220
Gly Glu Asn Gly Pro Pro Ser Ser Pro Asp Leu Asp Arg Ile Ala Ala
225 230 235 240
Ser Met Arg Ala Leu Val Leu Arg Glu Ala Glu Asp **Thr** Gln Val Phe
245 250 255
Gly Asp Leu Pro Arg Pro Arg Leu Asn **Thr** Ser Asp Phe Gln Lys Leu
260 265 270
Lys Arg Lys Tyr
275
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 3
LENGTH: 256
TYPE: PRT
ORGANISM: Homo. . . Glu Glu Leu Trp Glu Ala Val Val Gly Ala
1 5 10 15
Ala Glu Arg Phe Arg Ala Arg **Thr** Gly **Thr** Glu Leu Val Leu Leu
Thr
20 25 30
Ala Ala Pro Pro Pro Pro Arg Pro Gly Pro Cys Ala Tyr Ala Ala
35 40. . . Ala Glu Ala Ala Arg Arg Cys Leu His Asp
50 55 60
Ile Ala Leu Ala His Arg Ala Ala **Thr** Ala Ala Arg Leu Pro Ala Pro
65 70 75 80
Pro Pro Ala Pro Gln Pro Pro Ser Pro **Thr** Pro Ser Pro Pro Arg Pro
85 90 95
Thr Leu Ala Arg Glu Asp Asn Glu Glu Asp Glu Asp Glu Pro **Thr**
Glu
100 105 110
Thr Glu **Thr** Ser Gly Glu Gln Leu Gly Ile Ser Asp Asn Gly Gly
Leu
115 120 125
Phe Val Met Asp Glu Asp Ala **Thr** Leu Gln Asp Leu Pro Pro Phe Cys
130 135 140
Glu Ser Asp Pro Glu Ser **Thr** Asp Asp Gly Ser Leu Ser Glu Glu
Thr
145 150 155 160
Pro Ala Gly Pro Pro **Thr** Cys Ser Val Pro Pro Ala Ser Ala Leu Pro
165 170 175
Thr Gln Gln Tyr Ala Lys Ser Leu Pro Val Ser Val Pro Val Trp Gly
180 185 190
Phe Lys Glu Lys Arg **Thr** Glu Ala Arg Ser Ser Asp Gly Glu Asn Gly
195 200 205
Pro Pro Ser Ser Pro Asp Leu Asp Arg Ile Ala Ala Ser Met Arg Ala
210 215 220
Leu Val Leu Arg Glu Ala Glu Asp **Thr** Gln Val Phe Gly Asp Leu Pro
225 230 235 240
Arg Pro Arg Leu Asn **Thr** Ser Asp Phe Gln Lys Leu Lys Arg Lys Tyr
245 250 255
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 4
LENGTH: 20
TYPE: DNA
ORGANISM: Homo. . .

L12 ANSWER 6 OF 63 USPATFULL
ACCESSION NUMBER: 2001:102606 USPATFULL
TITLE: Synthetic mammalian .alpha.-n-acetylglucosaminidase and genetic sequences encoding same
INVENTOR(S): Hopwood, John Joseph, Stonyfell, Australia
Scott, Hamish Steele, Geneva, Switzerland
Weber, Birgit, Hackney, Australia
Blanch, Lianne, Grange, Australia
Anson, Donald Stewart, Thebarton, Australia
PATENT ASSIGNEE(S): Women's and Children's Hospital, Australia (non-U.S.

corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6255096	B1	20010703	
	WO 9719177		19970529	<--
APPLICATION INFO.:	US 1999-77354		19990422	(9)
	WO 1996-AU747		19961122	
			19990422	PCT 371 date
			19990422	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	AU 1995-6748	19951123

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Rao, Manjunath
LEGAL REPRESENTATIVE: Pokalsky, Ann R.
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1469
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6255096 B1 20010703
WO 9719177 19970529 <--
DRWD FIG. 1 is a photographic representation of .alpha.-N-acetylglucosaminidase purified from human **placenta** following SDS/PAGE. Lane 1: M.sub.r standards (kDa); Lanes 2 and 3: purified .alpha.-N-acetylglucosaminidase from human **placenta**. Lane 4 and 5, bovine serum albumin.
DRWD . . . I

Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	**Thr**	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V
Any residue	Xaa	X

DRWD . . . His

Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn; Gln
Ile	Leu; Val
Leu	Ile; Val
Lys	Arg; Gln; Glu
Met	Leu; Ile
Phe	Met; Leu; Tyr
Ser	**Thr**
Thr	Ser
Trp	Tyr
Tyr	Trp; Phe
Val	Ile; Leu

DETD . . . or guinea pig). Most preferably, the mammal is a human. Conveniently, the .alpha.-N-acetylglucosaminidase is isolatable from the liver, kidney or **placenta**. However, the present invention extends to all mammalian .alpha.-N-acetylglucosaminidase enzymes and

from any anatomical or cellular source and/or any biological. . .

DETD . . . SEQ ID NO:3 or a homologue, derivative or analogue thereof and the second primer molecule is preferably derived from the **antisense** strand of said gene.

DETD . . . for enzyme therapy may be by oral, intravenous, suppository, intraperitoneal, intramuscular, intranasal, intradermal or subcutaneous administration or by infusion or **implantation**. The .alpha.-N-acetylglucosaminidase is preferably as hereinbefore described including active mutants or derivatives thereof and glycosylation variants thereof. Administration may also. . .

DETD .alpha.-N-acetylglucosaminidase was purified according to the method described in Weber et al. (1996). Enzyme was purified to homogeneity from human **placenta**. Evidence of purity is shown following SDS/PAGE which is represented in FIG. 1. All samples were reduced with dithiothreitol prior. . .

DETD . . . show two polypeptides of about 82 kDa and 77 kDa molecular weight, which correspond to .alpha.-N-acetylglucosaminidase polypeptides purified from human **placenta** according to Example 1.

CLM What is claimed is:

5. The isolated nucleic acid molecule of claim 1 isolated from liver, kidney or **placenta**.

L12 ANSWER 7 OF 63 USPATFULL

ACCESSION NUMBER: 2001:71683 USPATFULL

TITLE: Persephin and related growth factors

INVENTOR(S): Johnson, Jr., Eugene M., St. Louis, MO, United States
Milbrandt, Jeffrey D., St. Louis, MO, United States
Kotzbauer, Paul T., Swarthmore, PA, United States
Lampe, Patricia A., St. Louis, MO, United States

PATENT ASSIGNEE(S): Washington University, St. Louis, MO, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6232449	B1	20010515	
	WO 9733911		19970918	<--
APPLICATION INFO.:	US 1998-981739		19980831	(8)
	WO 1997-US3461		19970314	
			19980831	PCT 371 date
			19980831	PCT 102(e) date

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-615944, filed on 14 Mar 1996, now abandoned

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Chan, Christina Y.

ASSISTANT EXAMINER: Hayes, Robert C.

LEGAL REPRESENTATIVE: Howell & Haferkamp, L.C.

NUMBER OF CLAIMS: 6

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 28 Drawing Figure(s); 27 Drawing Page(s)

LINE COUNT: 3790

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 6232449 B1 20010515
WO 9733911 19970918 <--

DETD . . . or Cys (SEQ ID NO:4); (2) with uncertainty as to positions 1, 2, 4, 10, 17 and 22, Xaa.sub.1 -Xaa.sub.2 -Val-Glu-Ala-Lys-Pro-Cys-Cys-Gly-Pro-**Thr**-Ala-Tyr-Glu-Asp-Xaa.sub.3 -Val-Ser-Phe-Leu-Ser-Val where Xaa.sub.1 and Xaa.sub.2 were unknown, Xaa.sub.3 was Gln or Glu (SEQ ID NO:5) and (3) Tyr-His-**Thr**-Leu-Gln-Glu-Leu-Ser-Ala-Arg (SEQ ID NO:6). Based upon these partial amino acid sequences, DNA probes and primers can be made and used to. . .

DETD . . . at specific receptors. For example, the receptors for TGF-.beta. and activins have been identified and make up a family of

Ser/**Thr** kinase transmembrane proteins (Kingsley, Genes and Dev 8:133-146, 1994; Bexk et al Nature 373:339-341, 1995 which are incorporated by reference).. . .

DETD Conserved-region amino acid sequences have been identified herein to include Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Tyr where Xaa.sub.1 is Ser, **Thr** or Ala and Xaa.sub.2 is Glu or Asp (SEQ ID NO:108); Glu-Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Arg-Tyr-Cys-Xaa.sub.4 -Gly-Xaa.sub.5 -Cys in which Xaa.sub.1 is **Thr**, Glu or lys, Xaa.sub.2 is Val, Leu or Ile, Xaa.sub.3 is Leu or Ile, Xaa.sub.4 is Ala or Ser, and. . . NO:113); and Cys-Cys-Xaa.sub.1 -Pro-Xaa.sub.2 -Xaa.sub.3 -Xaa.sub.4 -Xaa.sub.5 -Asp-Xaa.sub.6 -Xaa.sub.7 -Xaa.sub.8 -Phe-Leu-Asp-Xaa.sub.9 in which Xaa.sub.1 is Arg or Gln, Xaa.sub.2 is **Thr** or Val or Ile, Xaa.sub.3 is Ala or Ser, Xaa.sub.4 is Tyr or Phe, Xaa.sub.5 is Glu, Asp or Ala, Xaa.sub.6 is Glu, Asp or no amino acid, Xaa.sub.7 is val or leu, Xaa.sub.8 is Ser or **Thr**, and Xaa.sub.9 is Asp or Val (SEQ ID NO:114). Nucleotide sequences containing a coding sequence for the above conserved sequences. . .

DETD . . . anticipated to have at least a 62.5% identity with the consensus region octapeptide, Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Tyr where Xaa.sub.1 is Ser, **Thr** or Ala and Xaa.sub.2 is Glu or Asp (SEQ ID NO:108) or at least a 62.5 percent sequence identity with. . .

DETD . . . for mature persephin or neurturin protein. The term complementary to a nucleotide sequence in the context of persephin or neurturin **antisense** oligonucleotides and methods therefor means sufficiently complementary to such a sequence as to allow hybridization to that sequence in a cell, i.e., under physiological conditions. The persephin or neurturin **antisense** oligonucleotides preferably comprise a sequence containing from about 8 to about 100 nucleotides and more preferably the persephin or neurturin **antisense** oligonucleotides comprise from about 15 to about 30 nucleotides. The persephin or neurturin **antisense** oligonucleotides can also contain a variety of modifications that confer resistance to nucleolytic degradation such as, for example, modified internucleoside. . .

DETD . . . neurturin by the body. In one approach cells that secrete persephin or neurturin may be encapsulated into semipermeable membranes for **implantation** into a patient. The cells can be cells that normally express persephin or neurturin or a precursor thereof or the. . .

DETD . . . sequences from reverse transcribed MRNA. A forward primer (M1676; 5'-CCNACNGCNTAYGARGA, SEQ ID NO:50) corresponding to peptide sequence P2 Xaa.sub.1 -Xaa.sub.2 -Val-Glu-Ala-Lys-Pro-Cys-Cys-Gly-Pro-**Thr**-Ala-Tyr-Glu-Asp-Xaa.sub.3 -Val-Ser-Phe-Leu-Ser-Val where Xaa.sub.1 and Xaa.sub.2 were unknown, Xaa.sub.3 was Gln or Glu (SEQ ID NO:5) in combination with a reverse primer (M1677; 5'-ARYTCYTGNARNGTRTGRTA (SEQ ID NO:52) corresponding to peptide sequence P3 (Tyr-His-**Thr**-Leu-Gln-Glu-Leu-Ser-Ala-Arg) (SEQ ID NO:6) were used to amplify a 69 nucleotide product from cDNA templates derived from E21 rat and adult. . .

DETD . . . +

Spleen	-	+	
Cerebellum	-	-	
Uterus	++	-	
Bone marrow	++	-	
Testis	++	++	
Ovary	+	+	
Placenta	+	-	
Skeletal muscle	+	-	
Spinal cord	+	-	
Adrenal gland	++	++	
Gut	+	++	

DETD . . . probes or primers. Conserved-region amino acid sequences have been identified herein to include Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Tyr where Xaa.sub.1 is Ser, **Thr** or Ala and Xaa.sub.2 is Glu or Asp (SEQ ID NO:108); Glu-Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Arg-Tyr-Cys-Xaa.sub.4 -Gly-Xaa.sub.5 -Cys in which Xaa.sub.1 is **Thr**, Glu or lys, Xaa.sub.2 is Val, Leu or Ile, Xaa.sub.3 is Leu or Ile, Xaa.sub.4 is Ala or Ser, and. . . NO:113); and Cys-Cys-Xaa.sub.1 -Pro-Xaa.sub.2 -Xaa.sub.3 -Xaa.sub.4 -Xaa.sub.5 -Asp-Xaa.sub.6 -Xaa.sub.7 -Xaa.sub.8 -Phe-Leu-Asp-Xaa.sub.9 in which Xaa.sub.1 is Arg or Gln, Xaa.sub.2 is **Thr** or Val or Ile, Xaa.sub.3 is Ala or Ser, Xaa.sub.4 is Tyr or Phe, Xaa.sub.5 is Glu, Asp or Ala, Xaa.sub.6 is Glu, Asp or no amino acid, Xaa.sub.7 is val or leu, Xaa.sub.8 is Ser or **Thr**, and Xaa.sub.9 is Asp or Val (SEQ ID NO:114). Nucleotide sequences containing a coding sequence for the above conserved sequences. . .

DETD . . . (M3119): 5'-GTNDGNGANYTGGGNYTGGGNTA (SEQ ID NO:115) 23 nt which codes for the amino acid sequence, Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Tyr where Xaa.sub.1 is **Thr**, Ser or Ala and Xaa.sub.2 is Glu or Asp (SEQ ID NO:125);

DETD . . . acid sequence, Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Leu-Xaa.sub.4 -Xaa.sub.5 where Xaa.sub.1 is Asp or Glu, Xaa.sub.2 is Val or Leu, Xaa.sub.3 is **Thr** or Ser, Xaa.sub.4 is Asp or Glu, and Xaa.sub.5 is Asp or Val (SEQ ID NO:126);

DETD . . . acid sequence, Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Leu-Xaa.sub.4 -Xaa.sub.5 where Xaa.sub.1 is Asp or Glu, Xaa.sub.2 is Val or Leu, Xaa.sub.3 is **Thr** or Ser, Xaa.sub.4 is Asp or Glu, and Xaa.sub.5 is Asp or Val (SEQ ID NO:126);

DETD . . . (M3122): 5'-GTNDGNGANYTGGGNYTNGG (SEQ ID NO:119) 20 nt which codes for the amino acid sequence, Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly where Xaa.sub.1 is **Thr**, Ser or Ala and Xaa.sub.2 is Asp or Glu (SEQ ID NO:128); and

DETD . . . (M3176): 5'-GTNDGNGANYTGGGNYTGGGNTT (SEQ ID NO:120) 23 nt which codes for the amino acid sequence, Val-Xaa.sub.2 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Phe where Xaa.sub.1 is **Thr**, Ser or Ala and Xaa.sub.2 is Glu or Asp (SEQ ID NO:12 9).

DETD . . . acid sequence, Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Leu-Xaa.sub.4 -Xaa.sub.5 where Xaa.sub.1 is Asp or Glu, Xaa.sub.2 is Val or Leu, Xaa.sub.3 is **Thr** or Ser, Xaa.sub.4 is Asp or Glu, and Xaa.sub.1 is Asp or Val (SEQ ID NO:126);

DETD . . . acid sequence, Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Leu-Xaa.sub.4 -Xaa.sub.5 where Xaa.sub.1 is Asp or Glu, Xaa.sub.2 is Val or Leu, Xaa.sub.3 is **Thr** or Ser, Xaa.sub.4 is Asp or Glu, and Xaa.sub.5 is Asp or Val (SEQ ID NO:126);

DETD Primer 1, GTNWSNGANYTNGGNYTNGGNTA (SEQ ID NO:42) which encodes the amino acid sequence, Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Tyr where Xaa.sub.1 is Ser or **Thr** and Xaa.sub.2 is Glu or Asp (SEQ ID NO:33);

DETD . . . (SEQ ID NO:45) whose reverse complementary sequence encodes amino acid sequence Cys-Cys-Arg-Pro-Xaa.sub.1 -Ala-Xaa.sub.2 -Xaa.sub.3 -Asp-Xaa.sub.4 where Xaa.sub.1 is Ile or **Thr** or Val, Xaa.sub.2 Try or Phe, Xaa.sub.3 is Glu or Asp and Xaa.sub.4 is Glu or Asp (SEQ ID NO:38);

DETD Primer 6 GARRMNBTNHTNTTYMGNTAYTG (SEQ ID NO:47) which encodes amino acid sequence Glu-Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Arg-Tyr-Cys where Xaa.sub.1 is Glu or **Thr**, Xaa.sub.2 is Leu or Val and Xaa.sub.3 is Ile or Leu (SEO ID NO:40);

DETD . . . GARRMNBTNHTNTTYMGNTAYTGYDSNGGNDSNTGHGA (SEQ ID NO:48) which encodes amino acid sequence Glu-Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Arg-Tyr-Cys-Xaa.sub.4 -Gly-Xaa.sub.5 -Cys-Xaa.sub.6 where Xaa.sub.1 is Glu or **Thr**, Xaa.sub.2 is Leu or Val, Xaa.sub.3 is Ile or Leu, Xaa.sub.4 is Ser or Ala, Xaa.sub.5 is Ser or Ala. . .

DETD . . . is provided in greater detail as follows. Primers corresponding to the amino acid sequence Val-Xaa1-Xaa2-Leu-Gly-Leu-Gly-Tyr where Xaa1 is Ser or **Thr** and Xaa2 is Glu or Asp (SEQ ID NO:33) [M1996;

5'-GTNWSNGANYTNGGNYTNGGNTA (SEQ ID NO:42)] and Phe-Arg-Tyr-Cys-Xaa1-Gly-Xaa2-Cys-Xaa3-Xaa4-Ala where Xaa1 is Ala. . .

L12 ANSWER 8 OF 63 USPATFULL
ACCESSION NUMBER: 2001:60112 USPATFULL
TITLE: Transgenic non-human mammal expressing the DNA sequence encoding kappa casein mammary gland and milk
INVENTOR(S): Hansson, Lennart, Ume.ang., Sweden
Stromqvist, Mats, Ume.ang., Sweden
Bergstrom, Sven, Ume.ang., Sweden
Hernell, Olle, Ume.ang., Sweden
Tornell, Jan, Vastra, Sweden
PATENT ASSIGNEE(S): Symbicom Aktiebolag, Umea, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6222094	B1	20010424	
	WO 9315196		19930805	<--
APPLICATION INFO.:	US 1994-256799		19941206	(8)
	WO 1993-DK24		19930125	
			19941206	PCT 371 date
			19941206	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1992-88	19920123

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Crouch, Deborah
LEGAL REPRESENTATIVE: Cooper, Iver P.
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Figure(s); 18 Drawing Page(s)
LINE COUNT: 3140
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6222094 B1 20010424
WO 9315196 19930805 <--
SUMM . . . functions or by introduction of vectors encoding RNA sequences which are complementary to endogenous glycosyltransferase mRNA species, thereby function as **antisense** RNA.
SUMM Glycosylation is normally found in connection with amino acid residues Asn, Ser, **Thr** or hydroxylysine.
SUMM . . . this preferred embodiment, the fertilized oocytes are first microinjected by standard techniques. They are thereafter cultured in vitro until a "pre-**implantation** embryo" is obtained. Such pre-**implantation** embryos preferably contain approximately 16 to 150 cells. The 16 to 32 cell stage of an embryo is commonly referred to as a morula. Those pre-**implantation** embryos containing more than 32 cells are commonly referred to as blastocysts. They are generally characterized as demonstrating the development of a blastocoel cavity typically at the 64 cell stage. Methods for culturing fertilized oocytes to the pre-**implantation** stage include those described by Gordon et al. (1984), Methods in Enzymology, 101, 414; Hogan et al. (1986) in Manipulating. . . al (1984) J. Reprod. Fert. 72, 779-785; and Heyman, Y. et al. (1987) Theriogenology 27, 5968 (for bovine embryos). Such pre-**implantation** embryos are thereafter transferred to an appropriate female by standard methods to permit the birth of a transgenic or chimeric. . .
SUMM Since the frequency of transgene incorporation is often low, the detection of transgene integration in the pre-**implantation** embryo is highly desirable. In one aspect of the invention, methods are provided for identifying embryos wherein transgenesis has occurred and which permit **implantation** of transgenic embryos to form

transgenic animals. In this method, one or more cells are removed from the pre-**implantation** embryo. When equal division is used, the embryo is preferably not cultivated past the morula stage (32 cells). Division of the pre-**implantation** embryo (reviewed by Williams et al. (1984) Theriogenology 22, 521-531) results in two "hemi-embryos" (hemi-morula or hemi-blastocyst) one of which is capable of subsequent development after **implantation** into the appropriate female to develop in utero to term. Although equal division of the pre-**implantation** embryo is preferred, it is to be understood that such an embryo may be unequally divided either intentionally or unintentionally. . .

SUMM One of each of the hemi-embryos formed by division of pre-**implantation** embryos is analyzed to determine if the transgene has been integrated into the genome of the organism. Each of the other hemi-embryos is maintained for subsequent **implantation** into a recipient female of the species.

SUMM The identification of the pre-**implantation** embryos containing the integrated transgene is achieved by analyzing the DNA from one of each of the hemi-embryos. Such DNA. . . of the amplified DNA sequences, if any, and provides an indication of whether the transgene has been integrated into the pre-**implantation** embryo from which the hemi-embryo was obtained (now called a "transgenic hemi-embryo"). If it has, the remaining untreated transgenic hemi-embryo. . .

SUMM The above described methods for the detection of transgenesis in pre-**implantation** embryos provide economical and time saving methods for generating transgenic non-human animals since they significantly decrease the number of pregnancies. . .

SUMM In an alternate embodiment, the above described method for detecting transgenesis in pre-**implantation** embryos is combined with embryonic cloning steps to generate a clonal population of transgenic embryos which may thereafter be implanted. . .

SUMM . . . transgenic hemi-embryo is cultured in the same or in a similar medium as used to culture individual oocytes to the pre-**implantation** stage. The "transgenic embryo" so formed (preferably a transgenic morula) is then divided into "transgenic hemi-embryos" which can then be. . . a clonal population of two transgenic non-human animals. Alternatively, the two transgenic hemi-embryos obtained may be again cultivated to the pre-**implantation** stage, divided, and recultivated to the transgenic embryo stage. This procedure is repeated until the desired number of clonal transgenic. . .

SUMM . . . also be performed transvaginally and under echoscopic guidance. In this method, a needle is used to puncture the recipient animal's **placenta**, particularly the placentonal structures, which are fixed against the vaginal wall. Such sampling may be performed around day 60 of. . .

DETD . . . DNA were screened and analyzed. Human genomic libraries were obtained from Clontech (Palo Alto, USA). The libraries were constructed from **placenta** DNA (catalog #HL1067J) or female leukocyte DNA (catalog #HL1111J), cloned into .lambda.EMBL-3 vector. The average size of inserts are 15. . .

L12 ANSWER 9 OF 63 USPATFULL

ACCESSION NUMBER: 2000:18625 USPATFULL

TITLE: Transgenic non-human mammals producing EC-SOD protein in their milk

INVENTOR(S): Hansson, Lennart, Bjorkvagen 50, S-902 40 Ume.ang., Sweden

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6025540		20000215	
	WO 9500637		19950105	<--

APPLICATION INFO.: US 1995-556965 19951207 (8)
WO 1994-IB181 19940624
19951207 PCT 371 date
19951207 PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	DK 1993-753	19930624

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Priebe, Scott D.
ASSISTANT EXAMINER: Wilson, Michael C.
LEGAL REPRESENTATIVE: Cooper, Iver P.
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 2719
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6025540 20000215
WO 9500637 19950105 <--

SUMM . . . functions or by introduction of vectors encoding RNA sequences which are complementary to endogenous glycosyltransferase mRNA species, thereby function as **antisense** RNA.

SUMM . . . this preferred embodiment, the fertilized oocytes are first microinjected by standard techniques. They are thereafter cultured in vitro until a "pre-**implantation** embryo" is obtained. Such pre-**implantation** embryos preferably contain approximately 16 to 150 cells. The 16 to 32 cell stage of an embryo is commonly referred to as a morula. Those pre-**implantation** embryos containing more than 32 cells are commonly referred to as blastocysts. They are generally characterized as demonstrating the development of a blastocoel cavity typically at the 64 cell stage. Methods for culturing fertilized oocytes to the pre-**implantation** stage include those described by Gordon et al. [58]; Hogan et al. [41] (for the mouse embryo); and Hammer et. . . ovine embryos); and Eyestone et al. [62]; Camous et al. [63]; and Heyman et al. [64] (for bovine embryos). Such pre-**implantation** embryos are thereafter transferred to an appropriate female by standard methods to permit the birth of a transgenic or chimeric. . .

SUMM Since the frequency of transgene incorporation is often low, the detection of transgene integration in the pre-**implantation** embryo is highly desirable. In one aspect of the invention, methods are provided for identifying embryos wherein transgenesis has occurred and which permit **implantation** of transgenic embryos to form transgenic animals. In this method, one or more cells are removed from the pre-**implantation** embryo. When equal division is used, the embryo is preferably not cultivated past the morula stage (32 cells). Division of the pre-**implantation** embryo (reviewed by Williams et al. [65]) results in two "hemi-embryos" (hemi-morula or hemi-blastocyst) one of which is capable of subsequent development after **implantation** into the appropriate female to develop in utero to term. Although equal division of the pre-**implantation** embryo is preferred, it is to be understood that such an embryo may be unequally divided either intentionally or unintentionally. . .

SUMM One of each of the hemi-embryos formed by division of pre-**implantation** embryos is analyzed to determine if the transgene has been integrated into the genome of the organism. Each of the other hemi-embryos is maintained for subsequent **implantation** into a recipient female of the species.

SUMM The early identification of the pre-**implantation** embryos containing the integrated transgene is achieved by analyzing the DNA from one of each of the hemi-embryos. Such DNA. . . of the amplified DNA sequences, if any, and provides an indication of whether the transgene has been integrated into the pre-**implantation** embryo

from which the hemi-embryo was obtained (now called a "transgenic hemi-embryo"). If it has, the remaining untreated transgenic hemi-embryo. . .

SUMM The above described methods for the detection of transgenesis in pre-**implantation** embryos provide economical and time saving methods for generating transgenic non-human animals since they significantly decrease the number of pregnancies. . .

SUMM In an alternate embodiment, the above described method for detecting transgenesis in pre-**implantation** embryos is combined with embryonic cloning steps to generate a clonal population of transgenic embryos which may thereafter be implanted. . .

SUMM . . . transgenic hemi-embryo is cultured in the same or in a similar medium as used to culture individual oocytes to the pre-**implantation** stage. The "transgenic embryo" so formed (preferably a transgenic morula) is then divided into "transgenic hemi-embryos" which can then be. . . a clonal population of two transgenic non-human animals. Alternatively, the two transgenic hemi-embryos obtained may be again cultivated to the pre-**implantation** stage, divided, and recultivated to the transgenic embryo stage. This procedure is repeated until the desired number of clonal transgenic. . .

SUMM . . . also be performed transvaginally and under echoscopic guidance. In this method, a needle is used to puncture the recipient animal's **placenta**, particularly the placentonal structures, which are fixed against the vaginal wall. Such sampling may be performed around day 60 of. . .

DETD . . . - TGG ACG GGC GAG GAC TCG GCG GAG CCC AAC TC - #T GAC TCG GCG GAG

TGG 48
Trp **Thr** Gly Glu Asp Ser Ala Glu Pro Asn Se - #r Asp Ser Ala Glu Trp
1 5 - #. . . GTC ACG GAG AT - #C TGG CAG GAG GTC ATG
96
Ile Arg Asp Met Tyr Ala Lys Val **Thr** Glu Il - #e Trp Gln Glu Val Met
20 - # 25 - # 30
- - CAG CGG. . . GGC ACG CTC CAC GC - #C GCC TGC CAG GTG CAG
144
Gln Arg Arg Asp Asp Asp Gly **Thr** Leu His Al - #a Ala Cys Gln Val Gln
35 - # 40 - # 45
- - CCG. . . GCC ACG CTG GAC GCC GCG CAG CCC CG - #G GTG ACC GGC GTC GTC
192
Pro Ser Ala **Thr** Leu Asp Ala Ala Gln Pro Ar - #g Val **Thr**
Gly Val Val
50 - # 55 - # 60
- - CTC TTC CGG CAG CTT GCG CCC CGC. . . CCG ACC GAG CCG AAC AGC TC - #C
AGC CGC GCC ATC CAC
288
Leu Glu Gly Phe Pro **Thr** Glu Pro Asn Ser Se - #r Ser Arg Ala Ile His
85 - # 90 - # 95
-. . . TCC ACC GGG CCC
336
Val His Gln Phe Gly Asp Leu Ser Gln Gly Cy - #s Glu Ser **Thr** Gly Pro
100 - # 105 - # 110
- - CAC TAC AAC CCG CTG GCC GTG CCG CAC. . . linear
- - (ii) MOLECULE TYPE: protein
- - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #2:
- - Trp **Thr** Gly Glu Asp Ser Ala Glu Pro Asn Se - #r Asp Ser Ala Glu
Trp
1 5 - # 10 - # 15
- - Ile Arg Asp Met Tyr Ala Lys Val **Thr** Glu Il - #e Trp Gln Glu Val
Met
20 - # 25 - # 30
- - Gln Arg Arg Asp Asp Asp Gly **Thr** Leu His Al - #a Ala Cys Gln Val
Gln
35 - # 40 - # 45

- - Pro Ser Ala **Thr** Leu Asp Ala Ala Gln Pro Ar - #g Val **Thr**
Gly Val Val
50 - # 55 - # 60
- - Leu Phe Arg Gln Leu Ala Pro Arg. . . Phe Phe Ala
65 - # 70 - # 75 - # 80
- - Leu Glu Gly Phe Pro **Thr** Glu Pro Asn Ser Se - #r Ser Arg Ala Ile
His
85 - # 90 - # 95
- - Val His Gln Phe Gly Asp Leu Ser Gln Gly Cy - #s Glu Ser **Thr** Gly
Pro
100 - # 105 - # 110
- - His Tyr Asn Pro Leu Ala Val Pro His. . .

L12 ANSWER 10 OF 63 USPATFULL
ACCESSION NUMBER: 1999:170432 USPATFULL
TITLE: Polynucleotide encoding a novel purinergic P.sub.2U receptor
INVENTOR(S): Coleman, Roger, Mountain View, CA, United States
Au-Young, Janice, Berkeley, CA, United States
Stuart, Susan G., Montara, CA, United States
Guegler, Karl J., Menlo Park, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6008039		19991228	<--
APPLICATION INFO.:	US 1995-459046		19950602	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hutzell, Paula K.
ASSISTANT EXAMINER: Hayes, Robert C.
LEGAL REPRESENTATIVE: Luther, Barbara J., Billings, Lucy J.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1538
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6008039 19991228 <--
AB . . . invention provides nucleotide and amino acid sequences that identify and encode a novel purinergic P.sub.U2 receptor (PNR) expressed in human **placenta**. The present invention also provides for **antisense** molecules to the nucleotide sequences which encode PNR, expression vectors for the production of purified PNR, antibodies capable of binding. . .
SUMM . . . a short N-terminus with two conserved N-glycosylation sites, a moderately short third internal loop, and a long C-terminus containing a Ser/**Thr**-rich region. All adrenergic receptors elevate cAMP or intracellular calcium.
SUMM Purinergic receptors of the **placenta** are likely found on immune or vascular cells and appear to play an important role in signal transduction and other specialized functions of the **placenta** as briefly described below.
SUMM **Placenta**
SUMM The **placenta** is a thickened discoid temporary organ that acts as the site of interchange of substances between the maternal and fetal. . .
SUMM The **placenta** consists of a fetal part derived from the chorion, one of the extraembryonic surrounding membranes of the conceptus and of a maternal part (decidua basalis) derived from the region of endometrium that underlies the **implantation** site. The **placenta** is thus the only organ composed of cells derived from two individuals. The boundary between maternal and fetal tissues is marked by extracellular products of necrosis referred to as fibrinoid.

The anatomy of the human **placenta** is discussed in detail in Benirschke and Kaufmann, (1992) Pathology of the Human **Placenta** , Springer-Verlag, New York City, pp 542-635.

SUMM . . . that gives rise to the embryo and an outer, single layer of trophoblast cells that encloses the blastocyst cavity. Following **implantation**, trophoblasts become highly invasive, erode and attach to the secretory endometrium. This invasive process involves matrix-degrading metalloproteinases (MMPs) and tissue. . .

SUMM The chorion or fetal part of the **placenta** has a chorionic plate at the point where the chorionic villi arise. The finger-like villi extend into the endometrial lacuna. . .

SUMM . . . for IgG movement is similar to that of IgA across epithelia. The transport of various materials, particularly nutrients, by the **placenta** is reviewed in Smith et al (1992 Ann Rev Nutrition 12:183-206) and Schneider (1991 Reprod Fertil Dev 3:345-353). The **placenta** is more than a simple conduit for nutrients; it engages in considerable metabolic activity contributing to the quality and quantity. . .

SUMM The function of the endometrium is to support the **implantation** and development of the embryo. During each menstrual cycle, the most superficial layer or functionalis, undergoes dramatic changes in preparation. . .

SUMM **Implantation** induces a decidual response that is characterized by pronounced changes in the endometrial stroma. Fibroblast-like cells transform into large, active. . .

SUMM . . . for both estrogen and progesterone. The effects of estrogen and progesterone on the endometrium, both during the cycle and following **implantation**, are complemented and implemented by a variety of growth factors. Insulin-like growth factors (IGFs) have a major role in the. . .

SUMM . . . to and receives venous blood from the lacunae situated between the villi. Although the maternal blood vessels are open during **implantation**, the fetal vessels remain intact. Fetal and maternal blood do not mix, except on rare occasions at the end of. . .

SUMM At the end of a full-term pregnancy, the **placenta** has the shape of a thick disk. The umbilical cord usually arises from the center of the **placenta** and connects the circulation of the fetus with the fetal placental circulation. Fetal venous blood reaches the **placenta** through the two umbilical arteries which branch and ultimately give rise to the vessels of the chorionic villi. In these. . .

SUMM The **placenta** is permeable to several substances and normally transfers oxygen, water, electrolytes, carbohydrates, lipids, proteins, vitamins, hormones, antibodies, and some drugs. . .

SUMM Soon after **implantation**, fetal villi begin to control maternal physiology creating an optimal environment for fetal development. Immediately after **implantation**, the syncytiotrophoblast synthesizes human chorionic gonadotropin (HCG), a glycoprotein hormone that mimics the effects of luteinizing hormone (LH) through the. . .

SUMM . . . al (1992) Growth Factors 6:219-231). PDGF may play a role in cytotrophoblast proliferation. The action of various cytokines on the **placenta** is reviewed in Mitchell et al (1993 **Placenta** 14:249-275) and Rutanen (1993 Ann Med 25:343-347).

SUMM Pathology of the **Placenta**

SUMM . . . severe toxemia or eclampsia includes convulsions and coma which may jeopardize both mother and fetus. The pathological changes of the **placenta** found in PIH are decidual arteriolopathy, infarcts, abruptio **placenta**, and Tenney-Parker changes.

SUMM . . . unknown although it is certain that the disease relates to the presence of placental tissue, since the delivery of the **placenta** (or hydatidiform mole) ends the disease process. An obliterative thickening of arterial walls and a reduced number of small arteries. .

SUMM Many types of infections by viruses, bacteria, mycoplasmas, or parasites

cause pathological changes in the **placenta**. Infections may ascend from the endocervical canal, or they may reach the **placenta** through the maternal blood. Rarely are they acquired by amniocentesis, chorionic villus sampling, amnioscopy, percutaneous umbilical blood sampling, or intrauterine fetal transfusions. Some infections cause gross and microscopic changes of the **placenta** , while others leave few characteristic or specifically recognizable traces.

SUMM Other disorders of the **placenta** include, but are not limited to, abruptio placentae; **placenta** previa; placental or maternal floor infarction; **placenta** accreta, increta, and percreta; extrachorial placentas; chorangioma; chorangiosis; chronic villitis; placental villous edema; widespread fibrosis of the terminal villi; intervillous thrombi; hemorrhagic endovasculitis; erythroblastosis fetalis; and nonimmune fetal hydrops. The pathology of the human **placenta** and decidua is discussed in Benirschke and Kaufmann, (1992) Pathology of the Human **Placenta**, Springer-Verlag, New York City pp. 542-635, and in Naeye (1992), Disorders of the **Placenta**, Fetus, and Neonate: Diagnosis and Clinical Significance, Mosby Year Book, St. Louis Mo.

SUMM . . . P.sub.2U receptor (PNR). Incyte Clone No 179696 was used to identify and clone the full length cDNA (pnr) from the **placenta** cDNA library. The novel purinergic receptor which is the subject of this patent application was identified among the cDNAs derived. . .

SUMM . . . activated or inflamed cells and/or tissues with pnr nucleic acids, fragments or oligomers thereof. Aspects of the invention include the **antisense** DNA of pnr; cloning or expression vectors containing pnr; host cells or organisms transformed with expression vectors containing pnr; a. . .

DETD . . . a unique nucleotide sequence identifying a novel homolog of the human purinergic receptor which was first identified in a human **placenta** cDNA library. The sequence for pnr is shown in SEQ ID NO:1 and is homologous to the GenBank sequence, RNU09402. . . PNR are useful in investigations of and interventions in the normal and abnormal physiologic and pathologic processes which comprise the **placenta** 's role in immunity. Therefore, an assay for upregulated expression of PNR can accelerate diagnosis and proper treatment of conditions. . .

DETD The cDNA inserts from random isolates of the **placenta** library were sequenced in part. Methods for DNA sequencing are well known in the art. Conventional enzymatic methods employed DNA. . .

DETD Analysis of INHERIT.TM. results from randomly picked and sequenced portions of clones from **placenta** library identified Incyte 179696 as a homolog of the purinergic receptor RNU09402. The cDNA insert comprising Incyte 179696 was fully. . .

DETD . . . XL-PCR (Perkin Elmer) procedure. Primers were designed based on known sequence; one primer was synthesized to initiate extension in the **antisense** direction (XLR) and the other to extend sequence in the sense direction (XLS or XLF). The primers allowed the sequence. . .

DETD The **placenta** cDNA library was used as a template, and XLR and XLS primers were used to amplify sequences containing the gene. . .

DETD VI **Antisense** Analysis

DETD Knowledge of the correct, complete cDNA sequence of PNR enables its use as a tool for **antisense** technology in the investigation of gene function. Oligonucleotides, cDNA or genomic fragments comprising the **antisense** strand of pnr can be used either in vitro or in vivo to inhibit expression of the mRNA. Such technology is now well known in the art, and **antisense** molecules can be designed at various locations along the nucleotide sequences. By treatment of cells or whole test animals with such **antisense** sequences, the gene of interest can be effectively turned off. Frequently, the function of the gene can be ascertained by. . .

DETD . . . sequences constructed to interrupt transcription of a particular open reading frame, modifications of gene expression can be

obtained by designing **antisense** sequences to intron regions, promoter/enhancer elements, or even to trans-acting regulatory genes. Similarly, inhibition can be achieved using Hogeboom base-pairing. . .

DETD . . . amount or distribution of PNR or downstream products of an active signalling cascade. Since PNR was found in a human **placenta** library, it appears to be upregulated in cell types mainly involved in immune protection or defense.

DETD . . . acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

- - (ii) MOLECULE TYPE: cDNA

- - (vii) IMMEDIATE SOURCE:

(A) LIBRARY: **Placenta**

(B) CLONE: 179696

- - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

- - ATGGAATGGG ACAATGGCAC AGACCAGGCT CTGGGCTTGC CACCCACCAC CT -
#GTGTCTAC. . . (ii) MOLECULE TYPE: protein

- - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

- - Met Glu Trp Asp Asn Gly **Thr** Asp Gln Ala Le - #u Gly Leu Pro Pro
Thr

1 5 - # 10 - # 15

- - **Thr** Cys Val Tyr Arg Glu Asn Phe Lys Gln Le - #u Leu Leu Pro Pro
Val

20 - #. . . Ala Leu Pro Le - #u Asn Ile Cys Val Ile

35 - # 40 - # 45

- - **Thr** Gln Ile Cys **Thr** Ser Arg Arg Ala Leu Th - #r Arg
Thr Ala Val Tyr

50 - # 55 - # 60

- - **Thr** Leu Asn Leu Ala Leu Pro Asp Leu Leu Ty - #r Ala Cys Ser Leu
Pro

65 - #. . . #r Ala Asn Leu His Gly

100 - # 105 - # 110

- - Arg Ile Leu Phe Leu **Thr** Cys Ile Ser Phe Gl - #n Arg Tyr Leu Gly
Ile

115 - # 120 - # 125

-. . . # 135 - # 140

- - Trp Leu Val Cys Val Ala Val Trp Leu Ala Va - #l **Thr Thr**
Gln Cys Leu

145 1 - #50 1 - #55 1 -
#60

- - Pro **Thr** Ala Ile Phe Ala Ala **Thr** Gly Ile Gl - #n Arg
Asn Arg **Thr**
Val

165 - # 170 - # 175

- - Cys Tyr Asp Leu Ser Pro Pro Ala Leu Ala Th. . . - #r His Tyr Met Pro
Tyr

180 - # 185 - # 190

- - Gly Met Ala Leu **Thr** Val Ile Gly Phe Leu Le - #u Pro Phe Ala Ala
Leu

195 - # 200 - # 205

. . . Phe Gly Ile Se - #r Phe Leu Pro Phe
His

245 - # 250 - # 255

- - Ile **Thr** Lys **Thr** Ala Tyr Leu Ala Val Arg Se - #r
Thr Pro Gly Val Pro

260 - # 265 - # 270

- - Cys **Thr** Val Leu Glu Ala Phe Ala Ala Ala Ty - #r Lys Gly
Thr Arg Pro

275 - # 280 - # 285

- - Phe Ala Ser Ala Asn Ser Val Leu Asp Pro Il - #e Leu Phe Tyr Phe
Thr

290 - # 295 - # 300

- - Gln Lys Lys Phe Arg Arg Arg Pro His Glu Le - #u Leu Gln Lys Leu
Thr

305 3 - #10 3 - #15 3 - #20

- - Asp Lys Trp Gln Arg Gln Gly Arg
325

CLM What is claimed is:

. . . synthesis in an outward manner under PCR conditions, and wherein the first primer is capable of being extended in an **antisense** direction and the second primer is capable of being extended in a sense direction; and b) combining said first and. . .

=> d history

(FILE 'HOME' ENTERED AT 13:53:01 ON 04 DEC 2002)

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL, BIOSIS' ENTERED AT 13:53:17 ON 04 DEC 2002

L1 82751 S THR OR F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN R

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1635kxh

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 28	Oct 21	EVENTLINE has been reloaded
NEWS 29	Oct 24	BEILSTEIN adds new search fields
NEWS 30	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 31	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 32	Nov 18	DKILIT has been renamed APOLLIT
NEWS 33	Nov 25	More calculated properties added to REGISTRY
NEWS 34	Dec 02	TIBKAT will be removed from STN
NEWS 35	Dec 04	CSA files on STN

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NEWS LOGIN	Welcome Banner and News Items
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=> s thr or f2r or (coagulation factor II receptor) or (thrombin receptor) or (par()1) or (hpar()1)
L1 82751 THR OR F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN RECEPTOR) OR (PAR(W) 1) OR (HPAR(W) 1)

=> s l1 and (antisense or ribozyme or triplex)
5 FILES SEARCHED...
L2 8539 L1 AND (ANTISENSE OR RIBOZYME OR TRIPLEX)

=> s l1 (p) (antisense or ribozyme or triplex)
L3 587 L1 (P) (ANTISENSE OR RIBOZYME OR TRIPLEX)

=> s f2r or (coagulation factor II receptor) or (thrombin receptor) or (par()1) or (hpar()1)
L4 7436 F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN RECEPTOR) OR (PAR(W) 1) OR (HPAR(W) 1)

=> s l4 and (antisense or ribozyme or triplex)
L5 272 L4 AND (ANTISENSE OR RIBOZYME OR TRIPLEX)

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6 212 DUP REM L5 (60 DUPLICATES REMOVED)

=> s l6 and PY<2000
3 FILES SEARCHED...
L7 83 L6 AND PY<2000

=> d l7 ibib abs 1-30

L7 ANSWER 1 OF 83 MEDLINE
ACCESSION NUMBER: 2001670639 MEDLINE
DOCUMENT NUMBER: 21572906 PubMed ID: 11715477
TITLE: The inhibiting effect of **antisense thrombin receptor** gene on the proliferation of pig vascular smooth muscle cell.
AUTHOR: Zhang Q; Jiang Y; Liu D
CORPORATE SOURCE: Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037.
SOURCE: CHUNG-HUA I HSUEH TSA CHIH [CHINESE MEDICAL JOURNAL], **(1999 May)** 79 (5) 365-8.
Journal code: 7511141. ISSN: 0376-2491.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011122
Last Updated on STN: 20020123
Entered Medline: 20011221

AB OBJECTIVE: To search for an effective approach to prevent the formation of restenosis after angioplasty. METHODS: A recombinant eukaryotic expression plasmid vector containing partial **antisense thrombin receptor** (ATR) gene named pcDNA3/ATR was constructed using recombinant DNA technique. Mini-pig aorta injury model was established by over-sized balloon catheter combined with high cholesterol diet feeding and its aortic smooth muscle cells(ASMC) were cultured. The effect of ATR gene expression in mini pig ASMC proliferation and growth factor gene expression were studied by 3H-TdR incorporation and Northern blot. RESULTS: The DNA synthesis in pig ASMC could be inhibited by ATR gene expression (The DNA synthesis in normal ASMC was lowered by 41.8%, and that in ASMC from injured artery was lowered by (50.3%). The mRNA and protein synthesis of TR could be down regulated by ATR gene expression. The mRNA expression of PDGF-A chain and bFGF stimulated by fetal calf serum (FCS) with thrombin were both downregulated in pig ASMC with expressed ATR gene. CONCLUSION: ATR gene expression can inhibit the proliferation of pig ASMC, and this is induced by its inhibiting effect on TR and finaly the signal transduction in ASMC.

L7 ANSWER 2 OF 83 MEDLINE
ACCESSION NUMBER: 1999025943 MEDLINE
DOCUMENT NUMBER: 99025943 PubMed ID: 9808563
TITLE: Protease-activated receptor 1 (**PAR-1**) is required and rate-limiting for thrombin-enhanced experimental pulmonary metastasis.
AUTHOR: Nierodzik M L; Chen K; Takeshita K; Li J J; Huang Y Q; Feng X S; D'Andrea M R; Andrade-Gordon P; Karpatkin S
CORPORATE SOURCE: New York University Medical Center and Kaplan Cancer Center, New York, NY, USA.
SOURCE: BLOOD, **(1998 Nov 15)** 92 (10) 3694-700.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981221

AB Thrombin-treated tumor cells induce a metastatic phenotype in experimental pulmonary murine metastasis. Thrombin binds to a unique protease-activated

receptor (**PAR-1**) that requires N-terminal proteolytic cleavage for activation by its tethered end. A 14-mer **thrombin receptor** activation peptide (TRAP) of the tethered end induces the same cellular changes as thrombin. Four murine tumor cells (Lewis lung, CT26 colon CA, B16F10 melanoma, and CCL163 fibroblasts) contain **PAR-1**, as detected by reverse transcriptase-polymerase chain reaction (RT-PCR). B16F10 cells did not contain the two other thrombin receptors, PAR-3 and glycoprotein Ib. TRAP-treated B16F10 tumor cells enhance pulmonary metastasis 41- to 48-fold (n = 17). Thrombin-treated B16F10 cells transfected with full-length murine **PAR-1** sense cDNA (S6, S7, S14, and S22) enhanced their adhesion to fibronectin 1.5- to 2.4-fold (n = 5, P <.04), whereas thrombin-treated wild-type cells do not. S6 (adhesion index, 1.5-fold) and S14 (index, 2.4-fold) when examined by RT-PCR and Northern analysis showed minimal expression of **PAR-1** for S6 over wild-type and considerable expression for S14. Immunohistochemistry showed greater expression of **PAR-1** for S14 compared with wild-type or empty-plasmid transfected cells. In vivo experiments with the thrombin-treated S14 transfectant showed a fivefold to sixfold increase in metastases compared with empty-plasmid transfected thrombin-treated naive cells or S6 cells (n = 20, P =.0001 to .02). **Antisense** had no effect on thrombin-stimulated tumor mass. Thus, **PAR-1** ligation and expression enhances and regulates tumor metastasis.

L7 ANSWER 3 OF 83 MEDLINE
ACCESSION NUMBER: 1998364972 MEDLINE
DOCUMENT NUMBER: 98364972 PubMed ID: 9701242
TITLE: **Thrombin receptor** overexpression in malignant and physiological invasion processes.
AUTHOR: Even-Ram S; Uziely B; Cohen P; Grisaru-Granovsky S; Maoz M; Ginzburg Y; Reich R; Vlodavsky I; Bar-Shavit R
CORPORATE SOURCE: Department of Oncology, Hadassah-Hebrew University Hospital, Jerusalem, Israel.
SOURCE: NATURE MEDICINE, **(1998 Aug)** 4 (8) 909-14.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980903
Last Updated on STN: 19980903
Entered Medline: 19980825

AB Although the involvement of soluble and matrix-immobilized proteases in tumor cell invasion and metastasis is well recognized, the role of proteolytically activated cell surface receptors has not been elucidated. We report here that **thrombin receptor**, a member of the protease-activated receptor family, is preferentially expressed in highly metastatic human breast carcinoma cell lines and breast carcinoma biopsy specimens. Introduction of **thrombin receptor antisense** cDNA considerably inhibited the invasion of metastatic breast carcinoma cells in culture through a reconstituted basement membrane. During placental implantation of the human embryo, **thrombin receptor** is transiently expressed in the invading cytotrophoblasts. These results emphasize the involvement of **thrombin receptor** in cell invasion associated with tumor progression and normal embryonic development.

L7 ANSWER 4 OF 83 MEDLINE
ACCESSION NUMBER: 1998232195 MEDLINE
DOCUMENT NUMBER: 98232195 PubMed ID: 9572483
TITLE: Protein kinase C beta modulates thrombin-induced Ca2+ signaling and endothelial permeability increase.
AUTHOR: Vuong P T; Malik A B; Nagpala P G; Lum H
CORPORATE SOURCE: Department of Pharmacology, University of Illinois at

Chicago, College of Medicine, 60607-7174, USA.
CONTRACT NUMBER: HL 27016 (NHLBI)
HL 45638 (NHLBI)
HL 46350 (NHLBI)
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, **(1998 Jun)** 175 (3) 379-87.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980529
Last Updated on STN: 19980529
Entered Medline: 19980515

AB We investigated the function of the Ca2+-dependent protein kinase C (PKC) beta1 in the regulation of endothelial barrier property. Human dermal microvascular endothelial cells (HMEC-1) were transduced with full-length PKCbeta1 **antisense** (AS) cDNA or control pLNCX vector to generate stable cell lines (HMEC-AS and HMEC-pLNCX, respectively). Analyses indicated that HMEC-AS expressed the **antisense** PKCbeta1 transcript with decreased PKCbeta protein level (without a change in PKCalpha or PKCepsilon). The baseline transendothelial 125I-albumin clearance rates of HMEC-1, HMEC-pLNCX, and HMEC-AS were 5.0+/-0.5 x 10(-2), 6.8+/-0.4 x 10(-2), and 6.9+/-0.6 x 10(-2) microl/min, respectively. Activation of HMEC-1 and HMEC-pLNCX with phorbol 12-myristate 13-acetate (PMA) increased the rates to the respective 14.5+/-1.7 x 10(-2) microl/min and 16.9+/-2.8 x 10(-2) microl/min (corresponding to 191% and 149% increases over baseline). However, in HMEC-AS, PMA increased the rate to 9.8+/-1.0 x 10(-2) microl/min (42%). When HMEC-1 and HMEC-pLNCX were activated with thrombin, the rates increased to 10.8+/-1.4 x 10(-2) and 14.0+/-1.9 x 10(-2) microl/min, respectively (116% and 106%). In contrast, thrombin stimulation of HMEC-AS more than doubled the increase to 27.2+/-3.5 x 10(-2) microl/min (294%). Furthermore, the thrombin-induced peak increase in the [Ca2+]i in HMEC-AS was greater than in control cells. Fluorescence-activated cell sorter analysis of **thrombin receptor** expression indicated that the augmented thrombin-induced responses were not attributable to altered receptor density in HMEC-AS. These results indicate that PKCbeta functions in a negative feedback manner to inactivate thrombin-generated signals and thereby modulates the endothelial permeability increase. Because decreased PKCbeta expression significantly reduced the PMA-induced permeability increase, PKCbeta may downregulate **thrombin receptor** function upstream of PKC activation (i.e., Ca2+).

L7 ANSWER 5 OF 83 MEDLINE
ACCESSION NUMBER: 1998147082 MEDLINE
DOCUMENT NUMBER: 98147082 PubMed ID: 9486128
TITLE: Protein kinase C beta regulates heterologous desensitization of **thrombin receptor** (**PAR-1**) in endothelial cells.
AUTHOR: Yan W; Tiruppathi C; Lum H; Qiao R; Malik A B
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, University of Illinois, Chicago 60612, USA.
CONTRACT NUMBER: HL-27016 (NHLBI)
HL-45638 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1998 Feb)** 274 (2 Pt 1) C387-95.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980407

Last Updated on STN: 19980407
Entered Medline: 19980323

AB We studied the effects of protein kinase C (PKC) activation on endothelial cell surface expression and function of the proteolytically activated **thrombin receptor** 1 (**PAR-1**). Cell surface **PAR-1** expression was assessed by immunofluorescence (using anti-**PAR-1** monoclonal antibody), and receptor activation was assessed by measuring increases in cytosolic Ca2+ concentration in human dermal microvascular endothelial cells (HMEC) exposed to alpha-thrombin or phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA). Immunofluorescence showed that thrombin and TPA reduced the cell surface expression of **PAR-1**. Prior exposure of HMEC to thrombin for 5 min desensitized the cells to thrombin, indicating homologous **PAR-1** desensitization. In contrast, prior activation of PKC with TPA produced desensitization to thrombin and histamine, indicating heterologous **PAR-1** desensitization. Treatment of cells with staurosporine, a PKC inhibitor, fully prevented heterologous desensitization, whereas thrombin-induced homologous desensitization persisted. Depletion of PKC beta isozymes (PKC beta I and PKC beta II) by transducing cells with **antisense** cDNA of PKC beta I prevented the TPA-induced decrease in cell surface **PAR-1** expression and restored approximately 60% of the cytosolic Ca2+ signal in response to thrombin. In contrast, depletion of PKC beta isozymes did not affect the loss of cell surface **PAR-1** and induction of homologous **PAR-1** desensitization by thrombin. Therefore, homologous **PAR-1** desensitization by thrombin occurs independently of PKC beta isozymes, whereas the PKC beta-activated pathway is important in signaling heterologous **PAR-1** desensitization in endothelial cells.

L7 ANSWER 6 OF 83 MEDLINE

ACCESSION NUMBER: 97330161 MEDLINE
DOCUMENT NUMBER: 97330161 PubMed ID: 9186620
TITLE: Thrombin activates NF-kappa B through **thrombin receptor** and results in proliferation of vascular smooth muscle cells: role of thrombin in atherosclerosis and restenosis.
AUTHOR: Maruyama I; Shigeta K; Miyahara H; Nakajima T; Shin H; Ide S; Kitajima I
CORPORATE SOURCE: Department of Laboratory Medicine, Faculty of Medicine, University of Kagoshima, Japan.
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, **(1997 Apr 15)** 811 429-36.
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970721
Last Updated on STN: 19970721
Entered Medline: 19970708

AB We investigated the role of thrombin in the pathogenesis in atherosclerosis and restenosis. First we examined the effect of thrombin on cultured human vascular smooth muscle cells (VSMC). We showed that thrombin acts as a mitogen on VSMC through **thrombin receptor**. The expression of **thrombin receptor** was increased in the cell lines of VSMC established from directional coronary atherectomy (DCA). This is more pronounced in the cells from patients with restenosis after PTCA. Next we investigated the signaling pathway from thrombin/**thrombin receptor**. Thrombin activates **thrombin receptor** resulting in the exposing of the agonist peptide domain (**thrombin receptor** agonist peptide, TRAP). The signal from thrombin/**thrombin**

receptor activated protein C kinase, tyrosine kinase, and MAP kinase and resulted in NF-kappa B activation. Furthermore, treatment of the cells with **antisense** p65 oligodeoxynucleotides of NF-kappa B inhibited the thrombin-stimulated growth of VSMC in vitro. These results suggest that thrombin may have a role in the pathogenesis of atherosclerosis and restenosis after PTCA through the **thrombin receptor**.

L7 ANSWER 7 OF 83 MEDLINE
ACCESSION NUMBER: 97307623 MEDLINE
DOCUMENT NUMBER: 97307623 PubMed ID: 9164965
TITLE: Thrombin induces endothelial type II activation in vitro: IL-1 and TNF-alpha-independent IL-8 secretion and E-selectin expression.
AUTHOR: Kaplanski G; Fabrigoule M; Boulay V; Dinarello C A; Bongrand P; Kaplanski S; Farnarier C
CORPORATE SOURCE: Laboratory of Immunology, INSERM Unit 387, Hospital Sainte Marguerite, Marseille, France.
CONTRACT NUMBER: NIH 15614
SOURCE: JOURNAL OF IMMUNOLOGY, **(1997 Jun 1)** 158 (11) 5435-41.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970619
AB In addition to its role in coagulation, thrombin is involved in the inflammatory process by inducing vessel neutrophilic infiltration. Thrombin induces endothelial P-selectin expression and platelet activating factor release, which participate to induce early neutrophil adhesion and activation. We employed HUVEC and now show that thrombin induces the production of the chemokine IL-8 in a time- and dose-dependent fashion. Similarly, thrombin induced E-selectin expression on HUVEC. Both IL-8 secretion and E-selectin expression were preceded by an increase in steady state levels of the respective mRNAs. Thrombin action on HUVEC was inhibited by the specific thrombin inhibitor, hirudin. In addition, these effects of thrombin on HUVEC were mimicked by the 14-amino acid **thrombin receptor** agonist peptide, which triggers the native **thrombin receptor** in a similar fashion to thrombin itself. Although IL-1 and TNF-alpha also induce IL-8 and E-selectin, the thrombin effects in these experiments were not mediated by those cytokines, since neither IL-1 receptor antagonist nor anti-TNF-alpha Ab inhibited the effects of thrombin. Furthermore, IL-1alpha, IL-1beta, and TNF-alpha were not detected in the supernatants of thrombin-activated HUVEC. Although intracellular IL-1alpha was found in thrombin-activated HUVEC, **antisense** IL-1alpha had no inhibitory effect on IL-8 secretion. These results demonstrate that in addition to short term endothelial activation, thrombin also functions as a long acting proinflammatory agent by inducing endothelial synthesis of the mediators required for neutrophils activation and extravazation during inflammation.

L7 ANSWER 8 OF 83 MEDLINE
ACCESSION NUMBER: 97259279 MEDLINE
DOCUMENT NUMBER: 97259279 PubMed ID: 9105399
TITLE: Nonproteolytic activation of the **thrombin receptor** promotes human umbilical vein endothelial cell growth but not intracellular CA2+, prostacyclin, or permeability.
COMMENT: Erratum in: Biochem Pharmacol 1997 Jun 15;53(12):1945
AUTHOR: Schaeffer P; Riera E; Dupuy E; Herbert J M
CORPORATE SOURCE: Haemobiology Research Department, Sanofi Recherche,

Toulouse, France.
SOURCE: BIOCHEMICAL PHARMACOLOGY, **(1997 Feb 21)** 53 (4) 487-91.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970507
Last Updated on STN: 19980206
Entered Medline: 19970501

AB Both thrombin and the synthetic tetracapeptide **thrombin receptor**-activating peptide (TRAP), recently described as a peptide mimicking the new amino terminus created by cleavage of the **thrombin receptor**, stimulated the proliferation of human umbilical vein endothelial cells (HUVEC) in culture. Although to a lesser extent, F-14, a tetradecapeptide representing the residues 365-378 of human prothrombin, also promoted HUVEC growth, thereby demonstrating that thrombin can stimulate HUVEC growth via both a proteolytic and a nonenzymatic pathway. Thrombin-TRAP, and F-14-induced HUVEC growth were inhibited by a **thrombin receptor** oligodeoxynucleotide **antisense**, showing that the growth-inducing effects of all 3 compounds were mediated through the same **thrombin receptor**. Thrombin and TRAP also stimulated intracellular Ca2+ increase, monolayer permeability increase, and prostacyclin release in HUVEC. None of these effects was observed with F-14 suggesting that thrombin-induced intracellular Ca2+ release, permeability increase, and prostacyclin release in HUVEC required catalytic cleavage of the receptor, whereas thrombin-induced growth might also be due to activation of the **thrombin receptor** through a nonproteolytic pathway.

L7 ANSWER 9 OF 83 MEDLINE
ACCESSION NUMBER: 97162152 MEDLINE
DOCUMENT NUMBER: 97162152 PubMed ID: 9009139
TITLE: Intimal hyperplasia following vascular injury is not inhibited by an **antisense thrombin receptor** oligodeoxynucleotide.
AUTHOR: Herbert J M; Guy A F; Lamarche I; Mares A M; Savi P; Dol F
CORPORATE SOURCE: Haemobiology Research Department, Sanofi Recherche, Toulouse, France.
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, **(1997 Feb)** 170 (2) 106-14.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 19970306
Entered Medline: 19970224

AB Thrombin is a multifunctional serine protease with central functions in hemostasis, but demonstration of its role in the initiation and maintenance of cell proliferation which occurs following vascular injury is still lacking. To determine the role played by thrombin and its receptor in neointimal accumulation of smooth muscle cells in a rabbit carotid artery model, we have used an 18 mer **antisense** phosphorothioate oligonucleotide (ODN) directed against the translation initiation region of the human **thrombin receptor** gene. The **antisense** ODN inhibited in a dose-dependent manner thrombin- or **thrombin receptor** activating peptide-induced human aortic smooth muscle cell proliferation. The growth-inhibitory effect of **thrombin receptor antisense** ODN was preventable by an excess of sense oligomer and specific for thrombin. The

suppression of growth was accompanied by a marked decrease of the level of **thrombin receptor** expression as evidenced by [125I]-thrombin binding to smooth muscle cells. Under the same experimental conditions, the corresponding sense ODN was inactive. The effect of the **antisense** ODN on intimal smooth muscle hyperplasia in rabbit carotid arteries subjected to endothelial injury was then investigated. The topical application of the **antisense** (500 microg/artery) but not the sense ODN dissolved in F127 pluronic gel around the injured artery resulted, 2 weeks after the application, in a dramatic reduction of the expression of the **thrombin receptor** mRNA and protein levels as determined by in situ hybridization and immunohistochemistry. However, intimal smooth muscle cell accumulation as estimated by an intimal to medial cross-sectional area ratio was reduced only by 2.7% (vs. 10.3% for the sense ODN), whereas r-hirudin (200 microg/kg/day, s.c.), a potent direct thrombin inhibitor significantly reduced the formation of neointima in denuded carotid arteries (35.4% inhibition, P = 0.03).

L7 ANSWER 10 OF 83 MEDLINE
ACCESSION NUMBER: 96310865 MEDLINE
DOCUMENT NUMBER: 96310865 PubMed ID: 8684486
TITLE: A non-muscle myosin required for embryonic polarity in Caenorhabditis elegans.
AUTHOR: Guo S; Kemphues K J
CORPORATE SOURCE: Section of Genetics and Development, Cornell University, Ithaca, New York 14853, USA.
SOURCE: NATURE, **(1996 Aug 1)** 382 (6590) 455-8.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U49263
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960828
Last Updated on STN: 19960828
Entered Medline: 19960819

AB Daughter cells with distinct fates can arise through intrinsically asymmetrical divisions. Before such divisions, factors crucial for determining cell fates become asymmetrically localized in the mother cell. In Caenorhabditis elegans, PAR proteins are required for the early asymmetrical divisions that establish embryonic polarity, and are asymmetrically localized in early blastomeres, although the mechanism of their distribution is not known. Here we report the identification in C. elegans of nonmuscle myosin II heavy chain (designated NMY-2) by means of its interaction with the **PAR-1** protein, a putative Ser/Thr protein kinase. Furthermore, injections of nmy-2 **antisense** RNA into ovaries of adult worms cause embryonic partitioning defects and lead to mislocalization of PAR proteins. We therefore conclude the NMY-2 is required for establishing cellular polarity in C. elegans embryos.

L7 ANSWER 11 OF 83 MEDLINE
ACCESSION NUMBER: 96181571 MEDLINE
DOCUMENT NUMBER: 96181571 PubMed ID: 8601636
TITLE: The proteinase activated receptor-2 (PAR-2) mediates mitogenic responses in human vascular endothelial cells.
AUTHOR: Mirza H; Yatsula V; Bahou W F
CORPORATE SOURCE: Department of Medicine, State University of New York at Stony Brook, 11794-8151, USA.
CONTRACT NUMBER: R01HL02431 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, **(1996 Apr 1)** 97 (7) 1705-14.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960517
Last Updated on STN: 19960517
Entered Medline: 19960507

AB Proteolytically cleaved receptors, typified by the functional **thrombin receptor** (TR), represent a novel class of receptors that mediate signaling events by functional coupling to G proteins. Northern blot analysis completed with a human proteinase activated receptor-2 (PAR-2) cDNA as probe demonstrated the approximately 3.5kb PAR-2 transcript in total cellular RNA from human umbilical vein endothelial cells (HUVEC). Microspectrofluorimetry using Fura2-loaded HUVEC demonstrated a dose-dependent elevation in intracellular calcium transients ([Ca2+]i) to murine PAR39-44 (SLIGRL, putative neoligand after cleavage), with an approximate EC50 of 30 microM, and evidence for homologous desensitization with complete recovery at 45 min. Xenopus oocytes microinjected with TR cRNA failed to respond to 200 microM PAR39-44, and TR-targeted **antisense** oligonucleotides specifically abrogated thrombin-induced but not PAR39-44-mediated [Ca2+]i, excluding the possibility that TR/PAR-2 cell-surface coexpression was structurally linked. HUVEC incubated with PAR39-44 demonstrated a dose- and time-dependent mitogenic response similar to that seen with thrombin or TR42-47 (TR-activating peptide, SFLLRN). Preactivation of HUVEC with either PAR39-44 or thrombin resulted in heterologous desensitization to the corresponding agonist, an effect that was mediated primarily by TR internalization as evaluated by immunofluorescence and quantitative ELISA. These results ascribe a previously unrecognized function to the PAR-2 receptor, imply that a natural enzyme agonist may circulate in plasma, and suggest the presence of an additional regulatory mechanism controlling receptor activation events in vascular endothelial cells.

L7 ANSWER 12 OF 83 MEDLINE
ACCESSION NUMBER: 96025755 MEDLINE
DOCUMENT NUMBER: 96025755 PubMed ID: 7592574
TITLE: Selective inhibition of **thrombin receptor** -mediated Ca2+ entry by protein kinase C beta.
AUTHOR: Xu Y; Ware J A
CORPORATE SOURCE: Cardiovascular Division, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts 02215, USA.
CONTRACT NUMBER: HL02271 (NHLBI)
HL38820 (NHLBI)
HL47032 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1995 Oct 13)** 270 (41) 23887-90.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951204

AB Thrombin initiates many physiological processes in platelets and other megakaryocyte-lineage cells by interacting with surface receptors and generating rises in cytoplasmic Ca2+; these rises result from both Ca2+ release from intracellular stores and receptor-mediated Ca2+ entry. Regulators that limit Ca2+ entry after its initiation by thrombin have not been identified. In this study, prevention of expression of a single protein kinase C isoenzyme (PKC beta) by **antisense** cDNA overexpressed in HEL cells, a human megakaryoblastic cell line that expresses thrombin receptors, promotes **thrombin receptor** -mediated Ca2+ entry without altering thrombin-induced intracellular release of Ca2+. The cytoplasmic Ca2+ rise initiated by endoperoxide

analogs was not affected by inhibiting PKC beta. Overexpression of a cDNA encoding wild-type PKC beta mutated to prevent recognition by the **antisense** cDNA abolished the enhancement of Ca2+ influx following thrombin. Thus, PKC beta appears to be a specific negative regulator of **thrombin receptor**-mediated Ca2+ entry.

L7 ANSWER 13 OF 83 MEDLINE
ACCESSION NUMBER: 95302638 MEDLINE
DOCUMENT NUMBER: 95302638 PubMed ID: 7783334
TITLE: Study of signal transduction through **thrombin receptor** and anti-thrombotic strategy using its controls.
AUTHOR: Kitajima I
CORPORATE SOURCE: Department of Laboratory Medicine, Kagoshima University.
SOURCE: RINSHO KETSUEKI. JAPANESE JOURNAL OF CLINICAL HEMATOLOGY, **(1995 Apr)** 36 (4) 303-7.
Journal code: 2984782R. ISSN: 0485-1439.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950726
Last Updated on STN: 19970203
Entered Medline: 19950714

AB Thrombin, a key enzyme in the hemostatic pathway, also has various effects on the function of human platelet, endothelial cells (HUVEC) and vascular smooth muscle cells (VSMC). A **thrombin receptor** (TR) has been cloned and is thought to mediate a variety of thrombin-induced responses. The post-receptor signals are mediated by several protein kinases responsible for NF-kappa B activation, and most thrombin-inducible genes have the kappa B sequence in the regulatory elements. TR stimulation resulted in a biphasic activation of NF-kappa B and the late phase of which required new NF-kappa B synthesis. We showed that the **antisense** oligodeoxynucleotides (ODNs) of NF-kappa B have a marked inhibitory effect on thrombin-induced cellular responses. Furthermore, E5510, a compound with anti-platelet activity preferentially inhibited the thrombin-inducible NF-kappa B activation. Therapeutic potential of inhibition of TR-NF-kappa B activation signaling for treatment with thrombotic disease is also indicated.

L7 ANSWER 14 OF 83 MEDLINE
ACCESSION NUMBER: 95221403 MEDLINE
DOCUMENT NUMBER: 95221403 PubMed ID: 7706289
TITLE: Growth-related responses in arterial smooth muscle cells are arrested by **thrombin receptor** **antisense** sequences.
AUTHOR: Chaikof E L; Caban R; Yan C N; Rao G N; Runge M S
CORPORATE SOURCE: Department of Surgery (Vascular Division), Emory University School of Medicine, Atlanta, Georgia 30322, USA.
CONTRACT NUMBER: HL-02414 (NHLBI)
HL-48667 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1995 Mar 31)** 270 (13) 7431-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19950518
Entered Medline: 19950510

AB The capacity of **antisense** sequences to the **thrombin receptor** to selectively inhibit **thrombin**

receptor expression and limit mitogenic responses in vascular wall cells was investigated in vitro. Eight phosphorothioate oligodeoxynucleotides based on the sequences of the rat **thrombin receptor** (including sense, **antisense**, scrambled, and missense controls) were synthesized, characterized, and purified by high performance liquid chromatography. The **antisense** oligodeoxynucleotide (ODN 4) inhibitory effect was sequence-specific and both time-and concentration-dependent. A reduction in serum or alpha-thrombin-induced smooth muscle cell (SMC) proliferation was noted as early as 3 days at 30 microM (82%; 6.17 +/- 1.01 versus 34.08 +/- 3.89 x 10(4) cells/well; $p < 0.05$) and at a dose as low as 15 microM after 4 days in culture (19%; $p < 0.05$). Nonspecific effects were enhanced after prolonged exposure of SMC to the **antisense** oligodeoxynucleotide (> or = 6 days). A reduction of inositol phosphate generation greater than 50% ($p < 0.05$) was detected after exposure of SMC to **antisense** but not to sense or scrambled nucleotide sequences. This was observed after stimulation with both thrombin and SFFLRN (**thrombin receptor** peptide agonist). Northern blot analysis and enzyme-linked immunosorbent assays revealed 50 and 22% decreases, respectively, in **thrombin receptor** mRNA and protein (cell surface) levels in **antisense** oligonucleotide-treated (72 h) SMC as compared to untreated cells, suggesting that **thrombin receptor** down-regulation occurred at the pretranslational level. Thus, **thrombin receptor**-specific **antisense** sequences inhibit growth-related effects both of serum and thrombin on smooth muscle cells, potentially providing a new strategy for selective inhibition of receptor-mediated arterial injury responses.

L7 ANSWER 15 OF 83 MEDLINE
ACCESSION NUMBER: 95168175 MEDLINE
DOCUMENT NUMBER: 95168175 PubMed ID: 7863981
TITLE: Role of the **thrombin receptor** in restenosis and atherosclerosis.
COMMENT: Comment in: Am J Cardiol. 1995 Feb 23;75(6):63B-64B
AUTHOR: Baykal D; Schmedtje J F Jr; Runge M S
CORPORATE SOURCE: Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.
CONTRACT NUMBER: HL-02414 (NHLBI)
HL-48557 (NHLBI)
SOURCE: AMERICAN JOURNAL OF CARDIOLOGY, **(1995 Feb 23)** 75 (6) 82B-87B. Ref: 36
Journal code: 0207277. ISSN: 0002-9149.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950404
Last Updated on STN: 19950404
Entered Medline: 19950323

AB Thrombus generation is central to thrombosis at vascular lesion sites, including post-PCTA acute reocclusion and chronic restenosis. Thrombin stimulates platelet activation, monocyte and neutrophil chemotaxis, and endothelial production of prothrombotic factors. The varied physiologic effects of thrombin are due to the widespread presence of thrombin receptors in many cell types. The receptor is uniquely activated: thrombin binds to the receptor at the thrombin anion-binding exosite, the receptor ligand ("tethered ligand") apparently being a sequence of 6 amino acids (SFLLRN). Thus, peptides corresponding to the sequence of the tethered ligand can stimulate almost all functions of native thrombin itself. Several intracellular signaling pathways have been identified as important in the restenosis process: the G protein-related pathway, cyclic adenosine monophosphate (cAMP) mediator pathway, and tyrosine kinase activation

pathway. In situ hybridization has demonstrated an increase in **thrombin receptor** mRNA throughout the period of neointimal and vascular lesion development. The mechanism of this increase is unknown, but may be mediated by multiple inflammatory modulators. Several strategies have been tested in animal models for inhibiting thrombin: (1) Hirudin not only prevents thrombin from cleaving fibrinogen, but also prevents **thrombin receptor** activation. (2) **Thrombin receptor** antagonist peptides block platelet aggregation effects of thrombin. (3) Mono- and polyclonal antibodies inhibit **thrombin receptor** activation. (4) **Antisense** oligonucleotides block **thrombin receptor** expression.

L7 ANSWER 16 OF 83 MEDLINE
ACCESSION NUMBER: 95124328 MEDLINE
DOCUMENT NUMBER: 95124328 PubMed ID: 7823939
TITLE: Expression cloning of oncogenes by retroviral transfer of cDNA libraries.
AUTHOR: Whitehead I; Kirk H; Kay R
CORPORATE SOURCE: Department of Medical Genetics, University of British Columbia, Canada.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, **(1995 Feb)** 15 (2) 704-10.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950223
Last Updated on STN: 19980206
Entered Medline: 19950216

AB a cDNA library transfer system based on retroviral vectors has been developed for expression cloning in mammalian cells. The use of retroviral vectors results in stable cDNA transfer efficiencies which are at least 100-fold higher than those achieved by transfection and therefore enables the transfer and functional screening of very large libraries. In our initial application of retroviral transfer of cDNA libraries, we have selected for cDNAs which induce oncogenic transformation of NIH 3T3 fibroblasts, as measured by loss of contact inhibition of proliferation. Nineteen different transforming cDNAs were isolated from a total of 300,000 transferred cDNA clones. Three of these cDNAs were derived from known oncogenes (raf-1, lck, and ect2), while nine others were derived from genes which had been cloned previously but were not known to have the ability to transform fibroblasts (beta-catenin, **thrombin receptor**, phospholipase C-gamma 2 and Spi-2 protease inhibitor genes). The Spi-2 cDNA was expressed in **antisense** orientation and therefore is likely to act as an inhibitor of an endogenous transformation suppressor. Seven novel cDNAs with transforming activities, including those for three new members of the CDC24 family of guanine nucleotide exchange factors, were also cloned from the retroviral cDNA libraries. Retroviral transfer of libraries should be generally useful for cloning cDNAs which confer selectable phenotypes on many different types of mammalian cells.

L7 ANSWER 17 OF 83 MEDLINE
ACCESSION NUMBER: 95071419 MEDLINE
DOCUMENT NUMBER: 95071419 PubMed ID: 7980566
TITLE: Involvement of NF-kappa B activation in thrombin-induced human vascular smooth muscle cell proliferation.
AUTHOR: Nakajima T; Kitajima I; Shin H; Takasaki I; Shigeta K; Abeyama K; Yamashita Y; Tokioka T; Soejima Y; Maruyama I
CORPORATE SOURCE: Department of Laboratory Medicine, Faculty of Medicine, University of Kagoshima, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,

(1994 Oct 28) 204 (2) 950-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941130

AB A **thrombin receptor** has been cloned and is thought to mediate a variety of thrombin-induced responses. However, the transcription factors important for postreceptor signaling have been little clarified. The post-receptor signals are mediated by several protein kinases responsible for NF-kappa B activation, and most thrombin-inducible genes have the kappa B sequence in the regulatory elements. The possibility that NF-kappa B may participate in thrombin signaling was therefore investigated in cultured human vascular smooth muscle cells (VSMCs). **Thrombin receptor** stimulation resulted in activation of NF-kappa B. Furthermore, treatment of cells with **antisense** p65 ODNs of NF-kappa B inhibited thrombin-stimulated growth of VSMC in vitro. Results indicate that the activation of NF-kappa B is involved in thrombin signaling and that this pathway causes the proliferation of VSMC induced by thrombin. Therapeutic potential of **antisense** NF-kappa B ODNs for the treatment with atherosclerosis and restenosis is also indicated.

L7 ANSWER 18 OF 83 MEDLINE
ACCESSION NUMBER: 94380027 MEDLINE
DOCUMENT NUMBER: 94380027 PubMed ID: 8093037
TITLE: E5510 antagonizes **thrombin receptor** signals by inhibiting NF-kappa B activation.
AUTHOR: Nakajima T; Kitajima I; Shin H; Matsumoto W; Soejima Y; Maruyama I
CORPORATE SOURCE: Department of Laboratory Medicine, Faculty of Medicine, University of Kagoshima, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1994 Sep 15)** 203 (2) 1181-7.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941031
Last Updated on STN: 19970203
Entered Medline: 19941018

AB We have recently demonstrated that NF-kappa B is involved in a thrombin-signaling and that the **antisense** oligodeoxynucleotides (ODNs) of NF-kappa B has a marked inhibitory effect on thrombin-induced cellular responses. In this study, we demonstrate that E5510 (4-cyano-5,5-bis(methoxyphenyl)-4-pentenoic acid), a compound with anti-platelet activity preferentially inhibits the thrombin-inducible NF-kappa B activation and then antagonizes the following thrombin-induced cellular responses, proliferation and cytokines production in vascular smooth muscle cell, and the adherency of differentiated HL-60 cells. These data suggest that E5510 is an anti-atherosclerotic or anti-restenotic drug induced by thrombin.

L7 ANSWER 19 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:461098 CAPLUS
DOCUMENT NUMBER: 131:208829
TITLE: Effect of **antisense thrombin receptor** gene on the proliferation of human vascular smooth muscle cells

AUTHOR(S): Zhang, Qian; Meng, Xianmin; Jiang, Yuxin; Ding, Jinfeng; Tang, Jian; Chen, Guanghui
CORPORATE SOURCE: Gardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100037, Peop. Rep. China
SOURCE: Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao (**1999**), 15(3), 484-487
CODEN: ZSHXF2; ISSN: 1007-7626
PUBLISHER: Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao Bianweihui
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Restenosis after angioplasty severely limits the final effect of this therapeutic technique. To study the fundamental mechanisms of restenosis and search for an effectively preventive approach, an eukaryotic expression vector (pcDNA3/ATR) contg. a partial **antisense thrombin receptor** (ATR) gene was constructed by **antisense** RNA technique. The inhibition of the recombinant vector proliferation of cultured human aortic smooth muscle cells (ASMC) was studied after introducing pcDNA3/ATR into ASMC instantaneously. The results showed that 3H-TdR incorporation in the transfected human ASMC was inhibited with pcDNA3/ATR in a dose-dependent manner. The expression of a partial **antisense thrombin receptor** gene could inhibit the proliferation of human ASMC.

L7 ANSWER 20 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:421621 CAPLUS
DOCUMENT NUMBER: 129:159449
TITLE: Study of signal transduction through **thrombin receptor** in vascular smooth muscle cell
AUTHOR(S): Kitajima, Isao; Maruyama, Ikuo
CORPORATE SOURCE: Dep. Mol. Lab. Med., Kagoshima Univ., Kagoshima, Japan
SOURCE: Domyaku Koka (**1998**), 25(6/7), 225-229
CODEN: DOMKDM; ISSN: 0386-2682
PUBLISHER: Nippon Domyaku Koka Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 14 refs. Thrombin acts on the vascular endothelium to stimulate prodn. of plasminogen activator inhibitor and the potent smooth muscle cell mitogen platelet-derived growth factor, following proliferation of smooth muscle cell. A **thrombin receptor** has been cloned and is though to mediate a variety of thrombin-induced responses. The high expression of **thrombin receptor** in atherosclerotic lesions indicates a possible role **thrombin receptor** activation in restenosis and in atherogenesis itself. Cleavage of extracellular amino-terminus at this site is necessary and sufficient for receptor activation. The new amino terminus than function as a tethered ligand and stimulates receptor, which is essentially a peptide receptor predominantly by intramol. ligand, called as **thrombin receptor** activating peptide (TRAP). The post-receptor signals are studied. We obsd. increase of calcium influx and activation of protein kinase C (PKC) in cultured vascular smooth muscle cells stimulated by thrombin or TRAP. Next, the **thrombin receptor** signals are mediated by several protein kinases responsible for nuclear factor kappa B (NF-.kappa.B), and most thrombin-inducible genes have the .kappa.B sequence in the regulatory elements. Thrombin stimulation resulted in a biphasic activation of NF-.kappa.B, the early phase of which indicated nuclear translocation of NF-.kappa.B and the late phase of which required new synthesis. We showed that the **antisense** oligodeoxynucleotides of NF-.kappa.B have a marked inhibitory effect on thrombin-induced cellular responses. Furthermore, E5510, a compd. with anti-platelet activity preferentially inhibited the thrombin-inducible NF-.kappa.B activation. Thrombin inhibitors including thrombomodulin have been tried to prevent thrombin-mediated arteriosclerosis. Furthermore, therapeutic potential of

inhibition of **thrombin receptor**-NF-.kappa.B activation signaling for treatment such as **antisense** strategy is also indicated. Roles of thrombin and thrombin receptors in pathogenesis of atherosclerosis are also discussed.

L7 ANSWER 21 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:119221 CAPLUS
DOCUMENT NUMBER: 126:127885
TITLE: Cloning and cDNA sequence of human liver **thrombin receptor** homolog and its diagnostic and therapeutic uses
INVENTOR(S): Coleman, Roger; Au-young, Janice; Bandman, Olga; Seilhamer, Jeffrey J.
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640040	A2	19961219	WO 1996-US8948	19960604 <--
WO 9640040	A3	19970109		
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 5686597	A	19971111	US 1995-467125	19950606 <--
CA 2223077	AA	19961219	CA 1996-2223077	19960604 <--
AU 9659858	A1	19961230	AU 1996-59858	19960604 <--
AU 721194	B2	20000629		
EP 832128	A2	19980401	EP 1996-917198	19960604 <--
R: BE, DE, ES, FR, GB, IT, NL				
JP 11507519	T2	19990706	JP 1996-501392	19960604 <--
US 5869633	A	19990209	US 1997-911320	19970814 <--
US 6143870	A	20001107	US 1998-217101	19981221
US 2002128443	A1	20020912	US 2001-997522	20011128

PRIORITY APPLN. INFO.:

US 1995-467125	A	19950606
WO 1996-US8948	W	19960604
US 1997-911320	A3	19970814
US 1998-217101	A3	19981221
US 2000-643383	A1	20000821

AB The nucleotide and deduced amino acid sequences are provided for a novel **thrombin receptor** homolog (TRH), whose cDNA was identified and cloned from a human liver cDNA library. TRH is a 7-transmembrane receptor and is most similar to the human **thrombin receptor** identified by P. M. Dennington and M. C. Berndt (1994), as well as to residues 94-155 of the platelet activating factor receptor. The present invention also provides for **antisense** mols. to the nucleotide sequences which encode TRH, diagnostic tests based on TRH encoding nucleic acid mols., expression vectors for the prodn. of purified TRH, antibodies capable of binding to TRH, hybridization probes or oligonucleotides for the detection of TRH-encoding nucleotide sequences, genetically engineered host cells for the expression of TRH, and antagonists, antibodies and inhibitors which bind to the polypeptide TRH.

L7 ANSWER 22 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:299219 CAPLUS
DOCUMENT NUMBER: 125:6180
TITLE: Amyloid .beta.-peptide alters thrombin-induced calcium responses in cultured human neural cells

AUTHOR(S): Mattson, Mark P.; Begley, James G.
CORPORATE SOURCE: Sanders-Brown Research Center Aging, University Kentucky, Lexington, KY, 40536, USA
SOURCE: Amyloid (**1996**), 3(1), 28-40
CODEN: AIJIET; ISSN: 1350-6129
PUBLISHER: Parthenon Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The presence of prothrombin, thrombin receptors and thrombin inhibitors in the brain, together with recent evidence that thrombin can affect neuronal outgrowth and survival, suggests that thrombin signaling may be involved in neuronal plasticity and injury. In Alzheimer's disease (AD), thrombin is assocd. with plaques comprised largely of amyloid .beta.-peptide (A.beta.). Because recent studies have shown that A.beta. can destabilize neuronal calcium homeostasis, and because thrombin receptors are linked to inositol phospholipid hydrolysis and elevation of [Ca2+]i, we tested the hypothesis that A.beta. modifies [Ca2+]i responses to thrombin. Studies using **thrombin receptor** antibodies and **antisense** oligodeoxynucleotide technol. to suppress expression of thrombin receptors demonstrated that human SH-SY5Y neuroblastoma cells expressed thrombin receptors linked to Ca2+ release from intracellular stores. Relatively short term pretreatment (1 to 3 h) of the SH-SY5Y cells with A.beta.25-35 or A.beta.1-40 resulted in a significant two- to three-fold enhancement of thrombin-induced elevation of [Ca2+]i. In contrast, chronic pretreatment with A.beta.s (8 to 16 h) resulted in an attenuation or complete abrogation of [Ca2+]i responses to thrombin. Imaging of thiobarbituric acid fluorescence demonstrated that A.beta. induced lipid peroxidn., and the effects of both short and long term exposure to A.beta. on [Ca2+]i responses, were largely abrogated in cultures pretreated with antioxidants. Thus, A.beta. induces lipid peroxidn. which impairs **thrombin receptor**-mediated Ca2+ signaling. The data suggest that thrombin plays roles in neuronal plasticity and neurodegenerative processes, and A.beta. may induce aberrant thrombin signal transduction which could contribute to the pathogenesis of AD.

L7 ANSWER 23 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:42911 CAPLUS
DOCUMENT NUMBER: 124:83225
TITLE: Transgenic baby hamster kidney (BHK) cells induced for high expression of human **thrombin receptor** cDNA and use of **antisense** DNA for inhibiting **thrombin receptor**
INVENTOR(S): Takada, Masahiro; Ito, Osamu; Ogushi, Motoharu; Kobayashi, Hiroko; Yamada, Toshe; Tanaka, Hiroshi
PATENT ASSIGNEE(S): Eisai Co Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07289268	A2	19951107	JP 1994-109146	19940426 <--

AB BHK cells transformed with plasmid pK4K/hTR encoding human **thrombin receptor** are treated with basic fibroblast growth factor (bFGF) to induce high expression of the receptor. The system is useful in screening **antisense** DNA that are inhibitory to the receptors, which **antisense** DNA can be used for the prepn. of therapeutics or prophylactics for the diseases assocd. with the receptors. Inhibition of the bFGF-induced expression of human **thrombin receptor** by an **antisense** DNA was demonstrated.

L7 ANSWER 24 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:475667 CAPLUS
DOCUMENT NUMBER: 122:236436
TITLE: Role of the **thrombin receptor** in restenosis and atherosclerosis
AUTHOR(S): Baykal, Demir; Schmedtje, John F. Jr.; Runge, Marschall S.
CORPORATE SOURCE: School of Medicine, Emory University, Atlanta, GA, USA
SOURCE: American Journal of Cardiology (**1995**), 75(6), 82B-87B
CODEN: AJCDAG; ISSN: 0002-9149
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 36 refs. Thrombus generation is central to thrombosis at vascular lesion sites, including post-PCTA acute reocclusion and chronic restenosis. Thrombin stimulates platelet activation, monocyte and neutrophil chemotaxis, and endothelial prodn. of prothrombotic factors. The varied physiol. effects of thrombin are due to the widespread presence of thrombin receptors in many cell types. The receptor is uniquely activated: thrombin binds to the receptor at the thrombin anion-binding exosite, the receptor ligand ("tethered ligand") apparently being a sequence of 6 amino acids (SFLLRN). Thus, peptides corresponding to the sequence of the tethered ligand can stimulate almost all functions of native thrombin itself. Several intracellular signaling pathways have been identified as important in the restenosis process: the G protein-related pathway, cyclic adenosine monophosphate (cAMP) mediator pathway, and tyrosine kinase activation pathway. In situ hybridization has demonstrated an increase in **thrombin receptor** mRNA throughout the period of neointimal and vascular lesion development. The mechanism of this increase is unknown, but may be mediated by multiple inflammatory modulators. Several strategies have been tested in animal models for inhibiting thrombin: Hirudin not only prevents thrombin from cleaving fibrinogen, but also prevents **thrombin receptor** activation. **Thrombin receptor** antagonist peptides block platelet aggregation effects of thrombin. Mono- and polyclonal antibodies inhibit **thrombin receptor** activation. **Antisense** oligonucleotides block **thrombin receptor** expression.

L7 ANSWER 25 OF 83 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:423305 CAPLUS
DOCUMENT NUMBER: 115:23305
TITLE: Identification and analysis of **antisense** RNA target regions of the human immunodeficiency virus type 1
AUTHOR(S): Rittner, Karola; Sczakiel, Georg
CORPORATE SOURCE: Inst. Virusforsch., Dtsch. Krebsforschungszent., Heidelberg, D-6900, Germany
SOURCE: Nucleic Acids Research (**1991**), 19(7), 1421-6
CODEN: NARHAD; ISSN: 0305-1048
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Antisense** RNA, transcribed intracellularly from constitutive expression cassettes, inhibits the replication of the human immunodeficiency virus type 1 (HIV-1) as demonstrated by a quant. microinjection assay in human SW480 cells. Infectious proviral HIV-1 DNA was co-microinjected with a 5-fold molar excess of plasmids expressing **antisense** RNA complementary to a set of ten different HIV-1 target regions. The most inhibitory **antisense** RNA expression plasmids were targeted against a 1 kb region within the gag open reading frame and against a 562 base region contg. the coding sequences for the regulatory viral proteins tat and rev. Exptl. evidence is presented that the **antisense** principle is the inhibitory mechanism in this assay system.

L7 ANSWER 26 OF 83 LIFESCI COPYRIGHT 2002 CSA
ACCESSION NUMBER: 2000:24543 LIFESCI
TITLE: **Thrombin receptor** homolog polynucleotide
AUTHOR: Coleman, R.; Au-Young, J.; Bandman, O.; Seilhamer, J.
CORPORATE SOURCE: Incyte Pharmaceuticals, Inc.
SOURCE: (**19990209**) . US Patent: 5869633; US CLASS: 536/23.1; 536/24.5; 536/23.5; 530/350..
DOCUMENT TYPE: Patent
FILE SEGMENT: W3
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The present invention provides nucleotide and amino acid sequences that identify and encode a novel **thrombin receptor** homolog (TRH) expressed in human liver. The present invention also provides for **antisense** molecules to the nucleotide sequences which encode TRH, diagnostic tests based on TRH encoding nucleic acid molecules, expression vectors for the production of purified TRH, antibodies capable of binding specifically to TRH, hybridization probes or oligonucleotides for the detection of TRH-encoding nucleotide sequences, genetically engineered host cells for the expression of TRH, and antagonists, antibodies and inhibitors with specific binding activity for the polypeptide TRH.

L7 ANSWER 27 OF 83 USPATFULL
ACCESSION NUMBER: 2002:303872 USPATFULL
TITLE: Lipid kinase
INVENTOR(S): Vanhaesebroeck, Bart, London, UNITED KINGDOM
Waterfield, Michael Derek, London, UNITED KINGDOM
PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6482623	B1	20021119	
	WO 9746688		19971211	<--
APPLICATION INFO.:	US 1998-194640		19981201	(9)
	WO 1997-GB1471		19970530	
			19981201	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1996-11460	19960601

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Achutamurthy, Ponnathapu
ASSISTANT EXAMINER: Rao, Manjunath N.
LEGAL REPRESENTATIVE: Fulbright & Jaworski LLP
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 18 Drawing Page(s)
LINE COUNT: 1568

AB The invention relates to a novel lipid kinase which is part of the PI3 Kinase family. PI3 Kinases catalyze the addition of phosphate to inositol generating inositol mono, di and triphosphate. Inositol phosphates have been implicated in regulating intracellular signalling cascades resulting in alternations in gene expression which, amongst other effects, can result in cytoskeletal remodelling and modulation of cellular motility. More particularly the invention relates to a novel human PI3 Kinase, p110.delta. which interacts with p85, has a broad phosphoinositide specificity and is sensitive to the same kinase inhibitors as PI3 Kinase p110.alpha.. However in contrast to previously identified PI3 Kinases which show a ubiquitous pattern of expression, p110.delta. is selectively expressed in leucocytes. Importantly, p110.delta. shows enchanced expression in most melanomas tested and

therefore may play a crucial role in regulating the metastatic property exhibited by melanomas. The identification of agents that enhance or reduce p110.delta. activity may therefore prevent cancer metastasis.

L7 ANSWER 28 OF 83 USPATFULL
ACCESSION NUMBER: 2002:262057 USPATFULL
TITLE: Agents for the prevention of damages caused by stress conditions
INVENTOR(S): Bar-Shavit, Rachel, Jerusalem, ISRAEL
PATENT ASSIGNEE(S): Hadasit Medical Research Services & Development Limited, Jerusalem, ISRAEL (non-U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 6461611	B1	20021008		
	WO 9942483		19990826		<--
APPLICATION INFO.:	US 2000-600031		20000720	(9)	
	WO 1999-IL95		19990216		
			20000720	PCT 371 date	

	NUMBER	DATE
PRIORITY INFORMATION:	IL 1998-123349	19980218

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Tate, Christopher R.
ASSISTANT EXAMINER: Winston, Randall
LEGAL REPRESENTATIVE: Oliff & Berridge, PLC
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 634
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Pharmaceutical compositions for the treatment of a decrease in the levels of protease activated receptor (PAR) mRNA caused by a lack or decrease of oxygen level and/or a lack or decrease of blood flow including pharmaceutically acceptable carriers and activators of PAR are provided. Methods for prevention of a decrease in the levels of protease-activated receptor PAR mRNA caused by lack or decrease in the oxygen level and/or lack or decrease in blood flow are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 29 OF 83 USPATFULL
ACCESSION NUMBER: 2002:70095 USPATFULL
TITLE: Methods and compositions for inhibiting inflammation and angiogenesis comprising a mammalian CD97 .alpha. subunit
INVENTOR(S): Kelly, Kathleen, North Potomac, MD, United States
PATENT ASSIGNEE(S): The United States of America as represented by the Secretary of the Department of Health and Human Services, Washington, DC, United States (U.S. government)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 6365712	B1	20020402		
	WO 9817796		19980430		<--
APPLICATION INFO.:	US 1999-284819		19990820	(9)	
	WO 1997-US19772		19971024		
			19990820	PCT 371 date	

	NUMBER	DATE

PRIORITY INFORMATION: US 1996-27871P 19961025 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Huff, Sheela
ASSISTANT EXAMINER: Harris, Alana M.
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew LLP
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 3805
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated proteins comprising the T-cell surface antigen CD97 .alpha. are provided. Compositions and methods for making and detecting CD97 .alpha. are also provided. Further, the invention provides diagnostic and therapeutic methods and compositions for medical conditions involving CD97.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 30 OF 83 USPATFULL
ACCESSION NUMBER: 2001:196837 USPATFULL
TITLE: Human MEKK proteins, corresponding nucleic acid molecules, and uses therefor
INVENTOR(S): Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S): National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6312934	B1	20011106	
	WO 9947686		19990923	<--
APPLICATION INFO.:	US 2000-423890		20000306	(9)
	WO 1999-US5556		19990315	
			20000306	PCT 371 date
			20000306	PCT 102(e) date

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-78153P	19980316	(60)
	US 1998-99165P	19980904	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Monshipouri, M.
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP, Lauro, Esq, Peter C., Milasincic, Esq, Debra J.
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 35 Drawing Figure(s); 35 Drawing Page(s)
LINE COUNT: 2856
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated nucleic acid molecules encoding human MEKK proteins, and isolated MEKK proteins, are provided. The invention further provides **antisense** nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression vectors have been introduced and nonhuman transgenic animals carrying a human MEKK transgene. The invention further provides human MEKK fusion proteins and anti-human MEKK antibodies. Methods of using the human MEKK proteins and nucleic acid molecules of the invention are also disclosed, including methods for detecting human MEKK activity in a biological sample, methods of modulating human MEKK activity in a cell, and methods for identifying agents that modulate the activity of human MEKK.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d history

     (FILE 'HOME' ENTERED AT 13:53:01 ON 04 DEC 2002)

     FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL, BIOSIS' ENTERED AT
     13:53:17 ON 04 DEC 2002
L1         82751 S THR OR F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN R
L2          8539 S L1 AND (ANTISENSE OR RIBOZYME OR TRIPLEX)
L3           587 S L1 (P) (ANTISENSE OR RIBOZYME OR TRIPLEX)
L4          7436 S F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN RECEPTOR
L5           272 S L4 AND (ANTISENSE OR RIBOZYME OR TRIPLEX)
L6           212 DUP REM L5 (60 DUPLICATES REMOVED)
L7            83 S L6 AND PY<2000

=> s l2 and (placenta or implantation)
L8         2888 L2 AND (PLACENTA OR IMPLANTATION)

=> s l2 and (placenta)
L9         1989 L2 AND (PLACENTA)

=> s l2 and (placenta and implantation)
L10         439 L2 AND (PLACENTA AND IMPLANTATION)

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          436 DUP REM L10 (3 DUPLICATES REMOVED)

=> s l11 and py<2000
   3 FILES SEARCHED...
   5 FILES SEARCHED...
L12          63 L11 AND PY<2000

=> d l12 ibib abs 1-30

L12  ANSWER 1 OF 63     MEDLINE
ACCESSION NUMBER:    1998364972     MEDLINE
DOCUMENT NUMBER:     98364972   PubMed ID: 9701242
TITLE:               Thrombin receptor overexpression in
                     malignant and physiological invasion processes.
AUTHOR:              Even-Ram S; Uziely B; Cohen P; Grisaru-Granovsky S; Maoz M;
                     Ginzburg Y; Reich R; Vlodavsky I; Bar-Shavit R
CORPORATE SOURCE:    Department of Oncology, Hadassah-Hebrew University
                     Hospital, Jerusalem, Israel.
SOURCE:              NATURE MEDICINE, (1998 Aug) 4 (8) 909-14.
                     Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199808
ENTRY DATE:          Entered STN: 19980903
                     Last Updated on STN: 19980903
                     Entered Medline: 19980825
AB   Although the involvement of soluble and matrix-immobilized proteases in
     tumor cell invasion and metastasis is well recognized, the role of
     proteolytically activated cell surface receptors has not been elucidated.
     We report here that thrombin receptor, a member of the
     protease-activated receptor family, is preferentially expressed in highly
     metastatic human breast carcinoma cell lines and breast carcinoma biopsy
     specimens. Introduction of thrombin receptor
     antisense cDNA considerably inhibited the invasion of metastatic
     breast carcinoma cells in culture through a reconstituted basement
     membrane. During placental implantation of the human embryo,
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thrombin receptor is transiently expressed in the invading cytotrophoblasts. These results emphasize the involvement of **thrombin receptor** in cell invasion associated with tumor progression and normal embryonic development.

L12 ANSWER 2 OF 63 USPATFULL

ACCESSION NUMBER:	2002:303979 USPATFULL			
TITLE:	Use of neomycin for treating angiogenesis-related diseases			
INVENTOR(S):	Hu, Guo-fu, Brookline, MA, United States Vallee, Bert L., Boston, MA, United States			
PATENT ASSIGNEE(S):	Endowment for Research in Human Biology, Inc., Boston, MA, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6482802	B1	20021119	
	WO 9958126		19991118	<--
APPLICATION INFO.:	US 2000-700436		20001109	(9)
	WO 1999-US10269		19990511	
			20001109	PCT 371 date
	NUMBER		DATE	
PRIORITY INFORMATION:	US 1998-84921P		19980511	(60)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			
PRIMARY EXAMINER:	Raymond, Richard L.			
LEGAL REPRESENTATIVE:	Pennie & Edmonds LLP			
NUMBER OF CLAIMS:	63			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 4 Drawing Page(s)			
LINE COUNT:	2312			

AB The present invention is directed to using neomycin or an analogue thereof as an therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compositions comprising (a) neomycin or an analogue and, optionally, (b) another anti-angiogenic agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogues having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases.

L12 ANSWER 3 OF 63 USPATFULL

ACCESSION NUMBER:	2002:160542 USPATFULL			
TITLE:	Method of screening for a modulator of angiogenesis			
INVENTOR(S):	Lau, Lester F., Chicago, IL, United States			
PATENT ASSIGNEE(S):	Munin Corporation, Chicago, IL, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6413735	B1	20020702	
	WO 9733995		19970918	<--
APPLICATION INFO.:	US 1999-142569		19990402	(9)
	WO 1997-US4193		19970314	
			19990402	PCT 371 date
	NUMBER		DATE	
PRIORITY INFORMATION:	US 1996-13958P		19960315	(60)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			

PRIMARY EXAMINER: Crouch, Deborah
ASSISTANT EXAMINER: Woitach, Joseph T.
LEGAL REPRESENTATIVE: Katten Muchin Zavis
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 4088
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Polynucleotides encoding mammalian ECM signalling molecules affecting the cell adhesion, migration, and proliferation activities characterizing such complex biological processes as angiogenesis. chondrogenesis, and oncogenesis, are provided. The polynucleotide compositions include DNAs and RNAs comprising part, or all, of an ECM signalling molecule coding sequence, or biological equivalents. Polypeptide compositions are also provided. The polypeptide compositions comprise mammalian ECM signalling molecules, peptide fragments, inhibitory peptides capable of interacting with receptors for ECM signalling molecules, and antibody products recognizing Cyr61. Also provided are methods for producing mammalian ECM signalling molecules. Further provided are methods for using mammalian ECM signalling molecules to screen for, and/or modulate, disorders associated with angiogenesis, chondrogenesis, and oncogenesis; ex vivo methods for using mammalian ECM signalling molecules to prepare blood products are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 4 OF 63 USPATFULL
ACCESSION NUMBER: 2002:88222 USPATFULL
TITLE: Methods to diagnose a required regulation of trophoblast invasion
INVENTOR(S): Caniggia, Isabella, Toronto, CANADA
Post, Martin, 328 Wellesley Street East, Toronto, CANADA M4X 1H3
Lye, Stephen, Toronto, CANADA
PATENT ASSIGNEE(S): The Hospital for Sick Children (HSC), Toronto, CANADA (non-U.S. corporation)
Mount Sinai Hospital Corporation, Toronto, CANADA (non-U.S. corporation)
Post, Martin, Toronto, CANADA (non-U.S. individual)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6376199	B1	20020423	
	WO 9840747		19980917	<--
APPLICATION INFO.:	US 1999-380662		19991221	(9)
	WO 1998-CA180		19980305	
			19991221	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-39919P	19970307 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Eyler, Yvonne
ASSISTANT EXAMINER: Andres, Janet L.
LEGAL REPRESENTATIVE: Merchant & Gould P.C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1,9
NUMBER OF DRAWINGS: 19 Drawing Figure(s); 21 Drawing Page(s)
LINE COUNT: 2297
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods are provided for the diagnosis and treatment of patients with increased risk of preeclampsia. The methods involve measuring levels of TGF-.beta..sub.3, receptors of cytokines of the TG.beta. family, or

HIF-1.alpha..

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 5 OF 63 USPATFULL

ACCESSION NUMBER: 2002:63687 USPATFULL

TITLE: Prognostic compositions for prostate cancer and methods of use thereof

INVENTOR(S): Tricoli, James V., 106 Clover Leaf La., North Wales, PA, United States 19454
Rondinelli, Rachel, 418 Candlewood Way, Harleysville, PA, United States 19438

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6361948	B1	20020326	
	WO 9909215		19990225	<--
APPLICATION INFO.:	US 2000-485549		20001109	(9)
	WO 1998-US16768		19980813	
			20001109	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-55285P	19970813 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Horlick, Kenneth R.
LEGAL REPRESENTATIVE: Dean Dorfman Herrell & Skillman
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 1789

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a novel nucleic acid molecule, CLAR1, isolated from a human adult heart cDNA library. This cDNA is derived from a novel gene that represents a late stage-specific marker for prostate cancer progression. The CLAR1 cDNA, along with its encoded protein and antibodies thereto, provides a biological marker for aggressive prostate cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 6 OF 63 USPATFULL

ACCESSION NUMBER: 2001:102606 USPATFULL

TITLE: Synthetic mammalian .alpha.-n-acetylglucosaminidase and genetic sequences encoding same

INVENTOR(S): Hopwood, John Joseph, Stonyfell, Australia
Scott, Hamish Steele, Geneva, Switzerland
Weber, Birgit, Hackney, Australia
Blanch, Lianne, Grange, Australia
Anson, Donald Stewart, Thebarton, Australia

PATENT ASSIGNEE(S): Women's and Children's Hospital, Australia (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6255096	B1	20010703	
	WO 9719177		19970529	<--
APPLICATION INFO.:	US 1999-77354		19990422	(9)
	WO 1996-AU747		19961122	
			19990422	PCT 371 date
			19990422	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-55285P	19970813 (60)

PRIORITY INFORMATION: AU 1995-6748 19951123
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Rao, Manjunath
LEGAL REPRESENTATIVE: Pokalsky, Ann R.
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1469
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates generally to mammalian .alpha.-N-acetyglucosaminidase and to genetic sequences encoding same and to their use in the investigation, diagnosis and treatment of subjects suspected of or suffering from .alpha.-N-acetylglucosaminidase deficiency.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 7 OF 63 USPATFULL
ACCESSION NUMBER: 2001:71683 USPATFULL
TITLE: Persephin and related growth factors
INVENTOR(S): Johnson, Jr., Eugene M., St. Louis, MO, United States
Milbrandt, Jeffrey D., St. Louis, MO, United States
Kotzbauer, Paul T., Swarthmore, PA, United States
Lampe, Patricia A., St. Louis, MO, United States
PATENT ASSIGNEE(S): Washington University, St. Louis, MO, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6232449	B1	20010515	
	WO 9733911		19970918	<--
APPLICATION INFO.:	US 1998-981739		19980831	(8)
	WO 1997-US3461		19970314	
			19980831	PCT 371 date
			19980831	PCT 102(e) date

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-615944, filed on 14 Mar 1996, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Chan, Christina Y.
ASSISTANT EXAMINER: Hayes, Robert C.
LEGAL REPRESENTATIVE: Howell & Haferkamp, L.C.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 28 Drawing Figure(s); 27 Drawing Page(s)
LINE COUNT: 3790
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A novel growth factor, persephin, which belongs to the GDNF/neurturin family of growth factors, is disclosed. The mouse and rat amino acid sequences have been identified. Mouse and rat persephin genomic DNA sequences have been cloned and sequenced and the respective cDNA sequences identified. In addition, methods for treating degenerative conditions using persephin, methods for detecting persephin gene alterations and methods for detecting and monitoring patient levels of persephin are provided. Methods for identifying additional members of the persephin-neurturin-GDNF family of growth factors are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 8 OF 63 USPATFULL
ACCESSION NUMBER: 2001:60112 USPATFULL
TITLE: Transgenic non-human mammal expressing the DNA sequence encoding kappa casein mammary gland and milk

INVENTOR(S): Hansson, Lennart, Ume.ang., Sweden
Stromqvist, Mats, Ume.ang., Sweden
Bergstrom, Sven, Ume.ang., Sweden
Hernell, Olle, Ume.ang., Sweden
Tornell, Jan, Vastra, Sweden
PATENT ASSIGNEE(S): Symbicom Aktiebolag, Umea, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6222094	B1	20010424	
	WO 9315196		19930805	<--
APPLICATION INFO.:	US 1994-256799		19941206	(8)
	WO 1993-DK24		19930125	
			19941206	PCT 371 date
			19941206	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1992-88	19920123

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Crouch, Deborah
LEGAL REPRESENTATIVE: Cooper, Iver P.
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Figure(s); 18 Drawing Page(s)
LINE COUNT: 3140
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to an expression system comprising a DNA sequence encoding a polypeptide which ha a biological activity of human .kappa.-casein, the system comprising a 5'-flanking sequence capable of mediating expression of said DNA sequence. In preferred embodiments the 5'-flanking sequence is from a milk protein gene of a mammal such as a casein gene or whey acidic protein (WAP) gene and the DNA sequence contains at least one intron sequence. The invention further relates to DNA sequences, replicable expression vectors and cells harboring said vectors, recombinant polypeptide e.g. in glycosylated form, and milk, infant formula or nutrient supplement comprising recombinant polypeptide. The invention also relates to a method for producing a transgenic non-human mammal comprising injecting an expression system as defined above and optionally a further DNA encoding .beta.-casein or an analog, variant or subsequence thereof into a fertilized egg or a cell of an embryo of a mammal so as to incorporate the expression system into the germline of the mammal and developing the resulting injected fertilized egg or embryo into an adult female mammal. In one embodiment, the endogenous polypeptide expressing capability of the mammal is destroyed and/or replaced with the expression system defined above. The invention further relates to a transgenic non-human mammal such as a mouse, rat, rabbit, goat, sheep, pig, lama, camel or bovine species whose germ cells a somatic cells contain a DNA sequence as defined above as a result of chromosomal incorporation into the non-human mammalian genome, or into the genome of an ancestor of said non-human mammal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 9 OF 63 USPATFULL
ACCESSION NUMBER: 2000:18625 USPATFULL
TITLE: Transgenic non-human mammals producing EC-SOD protein in their milk
INVENTOR(S): Hansson, Lennart, Bjorkvagen 50, S-902 40 Ume.ang., Sweden

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 6025540	20000215		
	WO 9500637	19950105		<--
APPLICATION INFO.:	US 1995-556965	19951207	(8)	
	WO 1994-IB181	19940624		
		19951207	PCT 371 date	
		19951207	PCT 102(e) date	

	NUMBER	DATE
PRIORITY INFORMATION:	DK 1993-753	19930624

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Priebe, Scott D.
ASSISTANT EXAMINER: Wilson, Michael C.
LEGAL REPRESENTATIVE: Cooper, Iver P.
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 2719
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a transgenic non-human mammal comprising a DNA sequence encoding human extracellular superoxide dismutase (human EC-SOD) or a variant thereof which is expressed in the milk. Transgenic mice containing a chimeric whey acidic protein gene promoter operatively linked to human EC-SOD gene were produced. Levels of up to 0.7 mg human EC-SOD protein/mL milk were observed. The mammalian expression system is preferably expressed in a non-human mammal selected from the group containing rabbits, mice, rats, goats, sheep, pigs, llama, camels and bovine species. The human EC-SOD proteins dismutate superoxide radicals and bind heparin. Within the scope of the invention are also method for producing a transgenic non-human mammal capable of expressing human EC-SOD as defined above, and methods of making milk and methods of isolating protein from the milk.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 10 OF 63 USPATFULL
ACCESSION NUMBER: 1999:170432 USPATFULL
TITLE: Polynucleotide encoding a novel purinergic P.sub.2U receptor
INVENTOR(S): Coleman, Roger, Mountain View, CA, United States
Au-Young, Janice, Berkeley, CA, United States
Stuart, Susan G., Montara, CA, United States
Guegler, Karl J., Menlo Park, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6008039		19991228	<--
APPLICATION INFO.:	US 1995-459046		19950602	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hutzell, Paula K.
ASSISTANT EXAMINER: Hayes, Robert C.
LEGAL REPRESENTATIVE: Luther, Barbara J., Billings, Lucy J.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1538
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides nucleotide and amino acid sequences that identify and encode a novel purinergic P.sub.U2 receptor (PNR) expressed in human **placenta**. The present invention also provides for **antisense** molecules to the nucleotide sequences which encode

PNR, expression vectors for the production of purified PNR, antibodies capable of binding specifically to PNR, hybridization probes or oligonucleotides for the detection of PNR-encoding nucleotide sequences, genetically engineered host cells for the expression of PNR, and diagnostic tests based on PNR-encoding nucleic acid molecules or antibodies produced against the polypeptide PNR.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 11 OF 63 USPATFULL

ACCESSION NUMBER:	1999:170407 USPATFULL
TITLE:	Method of making lipid metabolic pathway compositions
INVENTOR(S):	Gimeno, Carlos J., Boston, MA, United States Acton, Susan, Jamaica Plain, MA, United States
PATENT ASSIGNEE(S):	Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6008014		19991228	<--
APPLICATION INFO.:	US 1996-707399		19960904	(8)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Burke, Julie
LEGAL REPRESENTATIVE:	Lahive & Cockfield, LLP, Mandragouras, Amy E.
NUMBER OF CLAIMS:	29
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT:	4049

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the discovery of novel genes encoding Lipid Metabolic Pathway (LMP) polypeptides. Therapeutics, diagnostics and screening assays based on these molecules are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 12 OF 63 USPATFULL

ACCESSION NUMBER:	1999:166981 USPATFULL
TITLE:	Methods for regulating gene expression
INVENTOR(S):	Bujard, Hermann, Heidelberg, Germany, Federal Republic of Gossen, Manfred, El Cerrito, CA, United States
PATENT ASSIGNEE(S):	BASF Aktiengesellschaft, Germany, Federal Republic of (non-U.S. corporation) BASF Bioresearch Corporation, Worcester, MA, United States (U.S. corporation) Knoll Aktiengelellschaft, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6004941		19991221	<--
APPLICATION INFO.:	US 1995-485740		19950607	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-383754, filed on 3 Feb 1995, now patented, Pat. No. US 5789156 And a continuation-in-part of Ser. No. US 1994-275876, filed on 15 Jul 1994, now patented, Pat. No. US 5654168 which is a continuation-in-part of Ser. No. US 1994-270637, filed on 1 Jul 1994, now abandoned And a continuation-in-part of Ser. No. US 1994-260452, filed on 14 Jun 1994, now patented, Pat. No. US 5650298 which is a continuation-in-part of Ser. No. US 1993-76327, filed on 14 Jun 1993, now abandoned And a continuation-in-part of Ser. No. US 1993-76726, filed on 14 Jun 1993, now patented, Pat. No. US 5464758

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Campell, Bruce R.
ASSISTANT EXAMINER: Nguyen, Dave Trong
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 4771
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of regulating gene expression in subjects using tetracycline-responsive fusion proteins are disclosed. In one embodiment, the method involves introducing into a cell the subject a nucleic acid molecule encoding a fusion protein which activates transcription, the fusion protein comprising a first polypeptide which binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which activates transcription in eukaryotic cells; and modulating the concentration of a tetracycline, or analogue thereof, in the subject. In another embodiment, the cell further comprises a fusion protein which inhibits transcription, the fusion protein comprising a first polypeptide which binds to a tet operator sequence, operatively linked to a second polypeptide which inhibits transcription in eukaryotic cells. In yet another embodiment, the method involves obtaining a cell from a subject, introducing into the cell a first nucleic acid molecule which operatively links a gene to at least one tet operator sequence, introducing into the cell a second nucleic acid molecule encoding a fusion protein of the invention to form a modified cell, administering the modified cell to the subject and modulating the concentration of a tetracycline, or analogue thereof, in the subject. The first and second nucleic acid molecules can be linked or can be separate molecules.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 13 OF 63 USPATFULL
ACCESSION NUMBER: 1999:166819 USPATFULL
TITLE: Embryogenesis protein
INVENTOR(S): Bandman, Olga, Mountain View, CA, United States
Lal, Preeti, Sunnyvale, CA, United States
Corley, Neil C., Mountain View, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6004778		19991221	<--
APPLICATION INFO.:	US 1997-904032		19970731	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Spector, Lorraine
ASSISTANT EXAMINER: Kaufman, Claire M.
LEGAL REPRESENTATIVE: Incyte Pharmaceuticals, Inc.
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Figure(s); 11 Drawing Page(s)
LINE COUNT: 2231
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a human embryogenesis protein (EMPRO) and polynucleotides which identify and encode EMPRO. The invention also provides expression vectors, host cells, agonists, antibodies and antagonists. The invention also provides methods for treating disorders associated with expression of EMPRO.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 14 OF 63 USPATFULL
ACCESSION NUMBER: 1999:163462 USPATFULL
TITLE: Polynucleotides encoding myeloid progenitor inhibitory factor-1 (MPIF-1) and polypeptides encoded thereby
INVENTOR(S): Ruben, Steven M., Olney, MD, United States
Li, Haodong, Gaithersburg, MD, United States
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6001606		19991214	<--
APPLICATION INFO.:	US 1996-722719		19960930	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-446881, filed on 5 May 1995, now abandoned which is a continuation-in-part of Ser. No. US 1995-465682, filed on 6 Jun 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-208339, filed on 8 Mar 1994, now patented, Pat. No. US 5504003 Ser. No. Ser. No. US 1995-468775, filed on 6 Jun 1995, now abandoned And Ser. No. WO 1996-US15592, filed on 27 Sep 1996 , said Ser. No. US 465682 which is a continuation-in-part of Ser. No. US 446881 , said Ser. No. US 468775 which is a continuation-in-part of Ser. No. US 446881

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-4517P	19950929 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Mertz, Prema
LEGAL REPRESENTATIVE: Sterne, Kessler, Goldstein & Fox, P.L.L.C.
NUMBER OF CLAIMS: 74
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 53 Drawing Figure(s); 49 Drawing Page(s)
LINE COUNT: 6406
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB There are disclosed therapeutic compositions and methods using isolated nucleic acid molecules encoding a human myeloid progenitor inhibitory factor-1 (MPIF-1) polypeptide (previously termed MIP-3 and chemokine .beta.8(CK.beta.8 or ckb-8)); a human monocyte-colony inhibitory factor (M-CIF) polypeptide (previously termed MIP1-.gamma. and chemokine .beta.1(CK.beta.1 or ckb-1)), and a macrophage inhibitory protein-4 (MIP-4), as well as MPIF-1, M-CIF and/or MIP-4 polypeptides themselves, as are vectors, host cells and recombinant methods for producing the same.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 15 OF 63 USPATFULL
ACCESSION NUMBER: 1999:159803 USPATFULL
TITLE: Receptor tyrosine kinase
INVENTOR(S): Breitman, Martin L., Willowdale, Canada
Rossant, Janet, Toronto, Canada
Dumont, Daniel J., Oakville, Canada
Yamaguchi, Terry P., Toronto, Canada
Breitman, Jo-Ann, Toronto, Canada executor of said Martin L. Breitman, deceased
PATENT ASSIGNEE(S): Mount Sinai Hospital Corporation, Toronto, Canada (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5998187		19991207	<--

APPLICATION INFO.: US 1997-838957 19970423 (8)
RELATED APPLN. INFO.: Division of Ser. No. US 1994-278089, filed on 20 Jul 1994, now patented, Pat. No. US 5687714 which is a continuation-in-part of Ser. No. US 1994-235408, filed on 29 Apr 1994, now abandoned which is a continuation-in-part of Ser. No. US 1992-921795, filed on 30 Jul 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Teng, Sally
LEGAL REPRESENTATIVE: Merchant & Gould P.C.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Figure(s); 70 Drawing Page(s)
LINE COUNT: 4316
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel receptor tyrosine kinase protein and isoforms thereof which are expressed in cells of the endothelial lineage, and DNA segments encoding the novel protein and isoforms thereof are disclosed. Methods for identifying ligands which are capable of binding to the receptor protein and methods for screening for agonist or antagonist substances of the interaction of the protein and a ligand are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 16 OF 63 USPATFULL
ACCESSION NUMBER: 1999:159786 USPATFULL
TITLE: Polynucleotides encoding hepatocyte-specific members of the FGF family
INVENTOR(S): Arakawa, Tsutomu, Thousand Oaks, CA, United States
Danilenko, Dimitry Michael, Camarillo, CA, United States
Itoh, Nobuyuki, Ohtsu, Japan
Martin, Francis Hall, Newbury Park, CA, United States
PATENT ASSIGNEE(S): Amgen Inc., Thousand Oaks, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5998170		19991207	<--
APPLICATION INFO.:	US 1997-943915		19971003	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Feisee, Lila
ASSISTANT EXAMINER: Saoud, Christine
LEGAL REPRESENTATIVE: Mazza, Richard J., Levy, Ron K., Odre, Steven M.
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 1898
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Nucleic acid molecules are described which are useful in vectors, transformed or transfected host cells, and methods for the recombinant expression of hepatocyte growth-specific polypeptide members of the FGF family.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 17 OF 63 USPATFULL
ACCESSION NUMBER: 1999:155514 USPATFULL
TITLE: Multidrug resistance-associated polypeptide
INVENTOR(S): Shyjan, Andrew, Nahant, MA, United States
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5994130		19991130	<--
APPLICATION INFO.:	US 1997-1273		19971231	(9)
RELATED APPLN. INFO.:	Division of Ser. No. US 1997-843459, filed on 16 Apr 1997			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Prouty, Rebecca E.			
ASSISTANT EXAMINER:	Hutson, Richard			
LEGAL REPRESENTATIVE:	Lahive & Cockfield, LLP			
NUMBER OF CLAIMS:	10			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 9 Drawing Page(s)			
LINE COUNT:	2956			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods are disclosed for improving the effectiveness of a chemotherapeutic regimen to eradicate multidrug-resistant transformed cells from the body of a mammal, preferably from the body of a human. The present disclosure capitalizes on the discovery of a novel multidrug-resistance associated protein (MRP), herein designated MRP-.beta.. The disclosed compositions include MRP-.alpha. nucleic acids, including probes and **antisense** oligonucleotides, MRP-.beta. polypeptides and antibodies, MRP-.beta. expressing host cells, and non-human mammals transgenic or nullizygous for MRP-.beta.. The disclosed methods include methods for attenuating aberrant MRP-.beta. gene expression, protein production and/or protein function. In addition, methods are disclosed for identifying and using a modulator, such as an inhibitor, of MRP-.beta.. Preferably, the modulator is a small molecule.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 18 OF 63 USPATFULL

ACCESSION NUMBER:	1999:151195 USPATFULL
TITLE:	GATA-6 transcription factor: compositions and methods
INVENTOR(S):	Walsh, Kenneth, Carlisle, MA, United States
PATENT ASSIGNEE(S):	St. Elizabeth's Medical Center, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5990092		19991123	<--
APPLICATION INFO.:	US 1997-927394		19970827	(8)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Degen, Nancy			
ASSISTANT EXAMINER:	Schwartzman, Robert			
LEGAL REPRESENTATIVE:	Wolf, Greenfield & Sacks P.C.			
NUMBER OF CLAIMS:	21			
EXEMPLARY CLAIM:	1			
LINE COUNT:	2449			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for reducing or preventing the proliferation of vascular smooth muscle cells are provided. The method involves the step of administering an isolated GATA-6 molecule to a subject to prevent or reduce vascular smooth muscle cell proliferation. The isolated GATA-6 molecule can be a GATA-6 nucleic acid or a GATA-6 protein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 19 OF 63 USPATFULL

ACCESSION NUMBER:	1999:141655 USPATFULL
TITLE:	Mammalian cell death preventing kinase, DPK
INVENTOR(S):	Xu, Hua, Thousand Oaks, CA, United States

PATENT ASSIGNEE(S): Amgen Inc., Thousand Oaks, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5981248		19991109	<--
APPLICATION INFO.:	US 1997-969630		19971113	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Sisson, Bradley L.
ASSISTANT EXAMINER: Bugaisky, Gabriele E.
LEGAL REPRESENTATIVE: Odre, S., Cook, R.
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Figure(s); 20 Drawing Page(s)
LINE COUNT: 2213
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are nucleic acids encoding novel proteins, designated DPK. Also disclosed are amino acid sequences for DPK polypeptides, methods for preparing DPK polypeptides, and other related aspects.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 20 OF 63 USPATFULL
ACCESSION NUMBER: 1999:132565 USPATFULL
TITLE: Diagnosis and treatment of AUR-1 and/or AUR-2 related disorders
INVENTOR(S): Plowman, Gregory, San Carlos, CA, United States
Mossie, Kevin, Gauteng, South Africa
PATENT ASSIGNEE(S): Sugen, Inc., Redwood City, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5972676		19991026	<--
APPLICATION INFO.:	US 1997-974655		19971119	(8)

RELATED APPLN. INFO.: Division of Ser. No. US 1996-755728, filed on 25 Nov 1996
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wax, Robert A.
LEGAL REPRESENTATIVE: Lyon & Lyon LLP
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1,7
LINE COUNT: 2323
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to AUR-1 and/or AUR-2 polypeptides, nucleic acids encoding such polypeptides, cells, tissues and animals containing such nucleic acids, antibodies to such polypeptides, assays utilizing such polypeptides, and methods relating to all of the foregoing. Methods for treatment, diagnosis, and screening are provided for AUR-1 and/or AUR-2 related diseases or conditions characterized by an abnormal interaction between a AUR-1 and/or AUR-2 polypeptide and a AUR-1 and/or AUR-2 binding partner.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 21 OF 63 USPATFULL
ACCESSION NUMBER: 1999:132542 USPATFULL
TITLE: Polynucleotides encoding a protein of embryogenesis
INVENTOR(S): Hillman, Jennifer L., Mountain View, CA, United States
Shah, Purvi, Sunnyvale, CA, United States
Corley, Neil C., Mountain View, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5972653		19991026	<--
APPLICATION INFO.:	US 1997-926724		19970910	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kemmerer, Elizabeth
ASSISTANT EXAMINER: Romeo, David S.
LEGAL REPRESENTATIVE: Incyte Pharmaceuticals, Inc., Streeter, David G.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 11 Drawing Page(s)
LINE COUNT: 2220
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a human protein of embryogenesis (PREM) and polynucleotides which identify and encode PREM. The invention also provides expression vectors, host cells, agonists, antibodies and antagonists. The invention also provides methods for treating disorders associated with expression of PREM.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 22 OF 63 USPATFULL
ACCESSION NUMBER: 1999:128386 USPATFULL
TITLE: Compositions and methods for the treatment and diagnosis of cardiovascular disease using rchd523 as a target
INVENTOR(S): Falb, Dean A., Wellesley, MA, United States
Gimbrone, Jr., Michael A., Jamaica Plain, MA, United States
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5968770		19991019	<--
APPLICATION INFO.:	US 1995-485573		19950607	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-386844, filed on 10 Feb 1995
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Low, Christopher S. F.
ASSISTANT EXAMINER: Nguyen, Dave Trong
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 40 Drawing Figure(s); 40 Drawing Page(s)
LINE COUNT: 5019
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods and compositions for the treatment and diagnosis of cardiovascular disease, including, but not limited to, atherosclerosis, ischemia/reperfusion, hypertension, restenosis, and arterial inflammation. Specifically, the present invention identifies and describes genes which are differentially expressed in cardiovascular disease states, relative to their expression in normal, or non-cardiovascular disease states, and/or in response to manipulations relevant to cardiovascular disease. Further, the present invention identifies and describes genes via the ability of their gene products to interact with gene products involved in cardiovascular disease. Still further, the present invention provides methods for the identification and therapeutic use of compounds as treatments of cardiovascular disease. Moreover, the present invention provides methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of cardiovascular disease, and for monitoring the

efficacy of compounds in clinical trials. Additionally, the present invention describes methods for the diagnostic evaluation and prognosis of various cardiovascular diseases, and for the identification of subjects exhibiting a predisposition to such conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 23 OF 63 USPATFULL

ACCESSION NUMBER: 1999:124708 USPATFULL
TITLE: Genetic sequences encoding glucocorticoid dehydrogenases and uses thereof
INVENTOR(S): Funder, John W., North Carlton, Australia
Albiston, Anthony L., North Balwyn, Australia
Obeyesekere, Varuni R., Malvern, Australia
Krozowski, Zygmunt S., Wheelers Hill, Australia
Smith, Robin E., Murrumbeena, Australia
PATENT ASSIGNEE(S): Baker Medical Research Institute, Victoria, Australia (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5965372		19991012	<--
APPLICATION INFO.:	US 1996-754369		19961122	(8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-519081, filed on 24 Aug 1995
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Huff, Sheela
ASSISTANT EXAMINER: Eyler, Yvonne
LEGAL REPRESENTATIVE: White, John P.Cooper & Dunham LLP
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 1428
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates generally to a nucleic acid molecule encoding, or complementary to a nucleic acid molecule encoding, a recombinant NAD+ dependent glucocorticoid dehydrogenase and more particularly to 11 .beta.-hydroxysteroid dehydrogenase-2 (11 .beta.HSD2). When expressed in a prokaryotic or eukaryotic cell, the nucleic acid molecule of the present invention is used to assay for potential agonists or antagonists of glucocorticoid dehydrogenase activity. Further, the present invention relates to immunoreactive molecules to NAD+ dependent glucocorticoid dehydrogenase which provide the basis for a new range of diagnostic agents for use, such as in the diagnosis and treatment of hypertension and in predicting the potential outcome of in vitro fertilisation and embryo transfer procedures.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 24 OF 63 USPATFULL

ACCESSION NUMBER: 1999:121224 USPATFULL
TITLE: Methods for modulation of cholesterol transport
INVENTOR(S): Kozarsky, Karen, Philadelphia, PA, United States
Rigotti, Attilio, Malden, MA, United States
Krieger, Monty, Needham, MA, United States
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, Cambridge, MA, United States (U.S. corporation)
The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5962322		19991005	<--
APPLICATION INFO.:	US 1996-749907		19961115	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Low, Christopher S. F.
LEGAL REPRESENTATIVE: Arnall Golden & Gregory, LLP
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1762
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for regulation of lipid and cholesterol uptake are described which are based on regulation of the expression or function of the SR-BI HDL receptor. The examples demonstrate that estrogen dramatically downregulates SR-BI under conditions of tremendous upregulation of the LDL-receptor. The examples also demonstrate the upregulation of SR-BI in rat adrenal membranes and other non-placental steroidogenic tissues from animals treated with estrogen, but not in other non-placental non-steroidogenic tissues, including lung, liver, and skin. Examples further demonstrate the uptake of fluorescently labeled HDL into the liver cells of animal, which does not occur when the animals are treated with estrogen. Examples also demonstrate the in vivo effects of SR-BI expression on HDL metabolism, in mice transiently overexpressing hepatic SR-BI following recombinant adenovirus infection. Overexpression of the SR-BI in the hepatic tissue caused a dramatic decrease in cholesterol blood levels. These results demonstrate that modulation of SR-BI levels, either directly or indirectly, can be used to modulate levels of cholesterol in the blood.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 25 OF 63 USPATFULL
ACCESSION NUMBER: 1999:121216 USPATFULL
TITLE: Calcium receptor-active molecules
INVENTOR(S): Brown, Edward M., Milton, MA, United States
Hebert, Steven C., Wellesley, MA, United States
Garrett, Jr., James E., Salt Lake City, UT, United States
PATENT ASSIGNEE(S): NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)
Brigham and Women's Hospital, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5962314		19991005	<--
APPLICATION INFO.:	US 1997-943986		19971003 (8)	

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-484565, filed on 7 Jun 1995, now patented, Pat. No. US 5763569 which is a continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994 which is a continuation-in-part of Ser. No. WO 1994-US12117, filed on 21 Oct 1994 Ser. No. Ser. No. US 1994-292827, filed on 19 Aug 1994, now abandoned Ser. No. Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned And Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ulm, John
ASSISTANT EXAMINER: Saoud, Christine
LEGAL REPRESENTATIVE: Lyon & Lyon LLP
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 111 Drawing Figure(s); 85 Drawing Page(s)
LINE COUNT: 7882
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the different roles inorganic ion

receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca.sup.2+ and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 26 OF 63 USPATFULL
ACCESSION NUMBER: 1999:121214 USPATFULL
TITLE: Diagnosis and treatment of AUR-1 and/or AUR-2 related disorders
INVENTOR(S): Plowman, Gregory, San Carlos, CA, United States
Mossie, Kevin, Gauteng, South Africa
PATENT ASSIGNEE(S): Sugen, Inc., Redwood City, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 5962312		19991005		<--
APPLICATION INFO.:	US 1996-755728		19961125	(8)	

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Lau, Kawai
LEGAL REPRESENTATIVE: Lyon & Lyon LLP
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 2310
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to AUR-1 and/or AUR-2 polypeptides, nucleic acids encoding such polypeptides, cells, tissues and animals containing such nucleic acids, antibodies to such polypeptides, assays utilizing such polypeptides, and methods relating to all of the foregoing. Methods for treatment, diagnosis, and screening are provided for AUR-1 and/or AUR-2 related diseases or conditions characterized by an abnormal interaction between a AUR-1 and/or AUR-2 polypeptide and a AUR-1 and/or AUR-2 binding partner.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 27 OF 63 USPATFULL
ACCESSION NUMBER: 1999:113643 USPATFULL
TITLE: Chromosome 18 marker
INVENTOR(S): Chen, Hong, Brookline, MA, United States
Freimer, Nelson B., San Francisco, CA, United States
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)
The Regents University of California, Oakland, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 5955355		19990921		<--
APPLICATION INFO.:	US 1997-828010		19970327	(8)	

	NUMBER	DATE

PRIORITY INFORMATION: US 1996-14498P 19960328 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hutzell, Paula K.
ASSISTANT EXAMINER: Pellegrino, Susan
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 2973
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the mammalian fsh05 gene, a novel gene associated with bipolar affective disorder (BAD) in humans. The invention encompasses fsh05 nucleic acids, recombinant DNA molecules, cloned genes or degenerate variants thereof, fsh05 gene products and antibodies directed against such gene products, cloning vectors containing mammalian fsh05 gene molecules, and hosts that have been genetically engineered to express such molecules. The invention further relates to methods for the identification of compounds that modulate the expression of fsh05 and to using such compounds as therapeutic agents in the treatment of fsh05 disorders and neuropsychiatric disorders. The invention also relates to methods for the diagnostic evaluation, genetic testing and prognosis of fsh05 disorders and neuropsychiatric disorders including schizophrenia, attention deficit disorder, a schizoaffective disorder, a bipolar affective disorder or a unipolar affective disorder, and to methods and compositions for the treatment these disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 28 OF 63 USPATFULL
ACCESSION NUMBER: 1999:113594 USPATFULL
TITLE: Genes encoding proteins that interact with the tub protein
INVENTOR(S): Gimeno, Carlos J., Wellesley, MA, United States
Errada, Patrick R., Cambridge, MA, United States
PATENT ASSIGNEE(S): Millenium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5955306		19990921	<--
APPLICATION INFO.:	US 1997-897340		19970721	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-715032, filed on 17 Sep 1996, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Railey, II, Johnny F.
LEGAL REPRESENTATIVE: Hanley, Elizabeth A., Mandragouras, Amy E.Lahive & Cockfield, LLP
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 4240
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the discovery of novel genes encoding Tub interactor (TI) polypeptides. Therapeutics, diagnostics and screening assays based on these molecules are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 29 OF 63 USPATFULL
ACCESSION NUMBER: 1999:99644 USPATFULL
TITLE: Methods and compositions for multiple gene transfer into bone cells
INVENTOR(S): Bonadio, Jeffrey, Ann Harbor, MI, United States

PATENT ASSIGNEE(S): Goldstein, Steven A., Ann Harbor, MI, United States
The Regent of The University of Michigan, Ann Arbor, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5942496		19990824	<--
APPLICATION INFO.:	US 1994-316650		19940930	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-199780, filed on 18 Feb 1994, now patented, Pat. No. US 5763416
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Campell, Bruce R.
ASSISTANT EXAMINER: Nguyen, Dave Trong
LEGAL REPRESENTATIVE: Arnold White & Durkee
NUMBER OF CLAIMS: 130
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 26 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 5310
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are methods, compositions, kits and devices for use in transferring nucleic acids into bone cells in situ and/or for stimulating bone progenitor cells. Type II collagen and, particularly, osteotropic genes, are shown to stimulate bone progenitor cells and to promote bone growth, repair and regeneration in vivo. Gene transfer protocols are disclosed for use in transferring various nucleic acid materials into bone, as may be used in treating various bone-related diseases and defects including fractures, osteoporosis, osteogenesis imperfecta and in connection with bone implants.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 30 OF 63 USPATFULL
ACCESSION NUMBER: 1999:99565 USPATFULL
TITLE: CD44-like protein and nucleic acids
INVENTOR(S): Ni, Jian, Rockville, MD, United States
Gentz, Reiner L., Silver Spring, MD, United States
Dillon, Patrick J., Gaithersburg, MD, United States
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5942417		19990824	<--
APPLICATION INFO.:	US 1997-892880		19970715	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-21762P	19960715 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Horlick, Kenneth R.
LEGAL REPRESENTATIVE: Sterne, Kessler, Goldstein & Fox P.L.L.C.
NUMBER OF CLAIMS: 87
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 3185
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention concerns a novel CD44-like protein receptor. In particular, isolated nucleic acid molecules are provided encoding the CD44-like protein. CD44-like polypeptides are also provided, as are screening methods for identifying agonists and antagonists capable of enhancing or inhibiting CD44-like protein-mediated signaling. The invention further concerns therapeutic methods for treating diseases associated with processes mediated by CD44-like protein signaling.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l12 ibib kwic 1-10

L12 ANSWER 1 OF 63 MEDLINE
ACCESSION NUMBER: 1998364972 MEDLINE
DOCUMENT NUMBER: 98364972 PubMed ID: 9701242
TITLE: **Thrombin receptor** overexpression in malignant and physiological invasion processes.
AUTHOR: Even-Ram S; Uziely B; Cohen P; Grisaru-Granovsky S; Maoz M; Ginzburg Y; Reich R; Vlodavsky I; Bar-Shavit R
CORPORATE SOURCE: Department of Oncology, Hadassah-Hebrew University Hospital, Jerusalem, Israel.
SOURCE: NATURE MEDICINE, **(1998 Aug)** 4 (8) 909-14.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980903
Last Updated on STN: 19980903
Entered Medline: 19980825

TI **Thrombin receptor** overexpression in malignant and physiological invasion processes.

SO NATURE MEDICINE, **(1998 Aug)** 4 (8) 909-14.
Journal code: 9502015. ISSN: 1078-8956.

AB . . . metastasis is well recognized, the role of proteolytically activated cell surface receptors has not been elucidated. We report here that **thrombin receptor**, a member of the protease-activated receptor family, is preferentially expressed in highly metastatic human breast carcinoma cell lines and breast carcinoma biopsy specimens. Introduction of **thrombin receptor antisense** cDNA considerably inhibited the invasion of metastatic breast carcinoma cells in culture through a reconstituted basement membrane. During placental **implantation** of the human embryo, **thrombin receptor** is transiently expressed in the invading cytotrophoblasts. These results emphasize the involvement of **thrombin receptor** in cell invasion associated with tumor progression and normal embryonic development.

CT . . .

ME, metabolism
Breast Neoplasms: ME, metabolism
*Breast Neoplasms: PA, pathology
Carcinoma: PA, pathology
Carcinoma, Infiltrating Duct: PA, pathology
Cell Line
***DNA, Antisense: PD, pharmacology**
DNA, Complementary
Gene Expression Regulation
Neoplasm Invasiveness
Neoplasm Metastasis: PA, pathology
Neoplasm Metastasis: PC, prevention & control
Ovum Implantation
***Placenta: PH, physiology**
Pregnancy
*Receptors, Thrombin: BI, biosynthesis
Receptors, Thrombin: PH, physiology
Recombinant Proteins: BI, biosynthesis
Transfection
Trophoblast: PH, physiology
Tumor. . .

CN 0 (DNA, **Antisense**); 0 (DNA, Complementary); 0 (Receptors,

Thrombin); 0 (Recombinant Proteins)

L12 ANSWER 2 OF 63 USPATFULL
ACCESSION NUMBER: 2002:303979 USPATFULL
TITLE: Use of neomycin for treating angiogenesis-related diseases
INVENTOR(S): Hu, Guo-fu, Brookline, MA, United States
Vallee, Bert L., Boston, MA, United States
PATENT ASSIGNEE(S): Endowment for Research in Human Biology, Inc., Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6482802	B1	20021119	
	WO 9958126		19991118	<--
APPLICATION INFO.:	US 2000-700436		20001109	(9)
	WO 1999-US10269		19990511	
			20001109	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-84921P	19980511 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Raymond, Richard L.
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 63
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 2312
PI US 6482802 B1 20021119
WO 9958126 19991118 <--
SUMM . . . development, development and growth of normal tissues and organs, wound healing, and the formation of the corpus luteum, endometrium and **placenta**.
SUMM . . . include the C-terminal peptides of angiogenin (Rybak et al., 1989, Biochem. Biophys. Res. Comm. 162:535-543), the ribonuclease inhibitor from human **placenta** (Lee et al., 1988, Biochemistry 27:8545-8553, Shapiro et al., 1987, Proc. Natl. Acad Sci. USA 84:2238-2241) and, more recently, a. . .
DETD . . . Proc. Natl. Acad. Sci. USA 84:2238-2241); actin and fragments thereof that interferes with angiogenin interaction with its receptor, such as NH.sub.2-Tyr-Ser-Val-Trp-Ile-Gly-Gly-Ser-Ile-Leu-Ala-Ser-Leu-Ser-**Thr**-Phe-Gln-Gln-Met-Trp-Ile-Ser-Lys-COOH (SEQ ID NO: 4) and derivatives thereof (Hu et al., Proc. Natl. Acad. Sci. USA 90:1217-1221); nucleotides that inhibit the. . .
DETD Compositions of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by **implantation** (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric. . .
DETD . . . in athymic mice has been used extensively to show that angiogenin antagonists such as monoclonal antibodies, its binding protein and **antisense** DNA, prevent the establishment of human tumor cells in mice (Olson et al., 1998, Proc. Am. Assoc. Cancer Res. 39:665A;. . .
DETD
GENERAL INFORMATION:
NUMBER OF SEQ ID NOs: 5
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 1
LENGTH: 11
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:

OTHER INFORMATION: deduced from **antisense** RNA corresponding to the receptor-binding stie of angiogenin in 5'->3' direction
SEQUENCE: 1
Val Phe Ser Val Arg Val Ser Ile Leu Val Phe
1 5 10
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 2
LENGTH: 13
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: deduced from **antisense** RNA corresponding to the receptor-binding stie of angiogenin in 3'->5' direction
SEQUENCE: 2
Leu Leu Phe Leu Pro Leu Gly Val Ser. . . NO: 4
LENGTH: 23
TYPE: PRT
ORGANISM: Homo Sapiens
SEQUENCE: 4
Tyr Ser Val Trp Ile Gly Gly Ser Ile Leu Ala Ser Leu Ser **Thr** Phe
1 5 10 15
Gln Gln Met Trp Ile Ser Lys
20
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 5
LENGTH: 44
TYPE: DNA
ORGANISM: Homo Sapiens
SEQUENCE:. . .
CLM What is claimed is:
. . . ID NO. 1), peptide comprising the sequence NH.sub.2-Leu-Leu-Phe-Leu-Pro-Leu-Gly-Val-Ser-Leu-Leu-Asp-Ser-COOH (SEQ ID NO. 2), human placental ribonuclease inhibitor, peptide comprising the sequence NH.sub.2-Tyr-Ser-Val-Trp-Ile-Gly-Gly-Ser-Ile-Leu-Ala-Ser-Leu-Ser-**Thr**-Phe-Gln-Gln-Met-Trp-Ile-Ser-Lys-COOH (SEQ ID NO. 4), peptide comprising the sequence NH.sub.2-Ala-Gln-Leu-Ala-Gly-Glu-Cys-Arg-Glu-Asn-Val-Cys-Met-Gly-Ile-Glu-Gly-Arg-COOH (SEQ ID NO. 3), nucleotide comprising the sequence 5'-CGGACGAATGCTTTGATGTTGTGCTGGACCAGCGTTCATTCTCA-3' (SEQ ID. . .
. . . ID NO. 1), peptide comprising the sequence NH.sub.2-Leu-Leu-Phe-Leu-Pro-Leu-Gly-Val-Ser-Leu-Leu-Asp-Ser-COOH (SEQ ID NO. 2), human placental ribonuclease inhibitor, peptide comprising the sequence NH.sub.2-Tyr-Ser-Val-Trp-Ile-Gly-Gly-Ser-Ile-Leu-Ala-Ser-Leu-Ser-**Thr**-Phe-Gln-Gln-Met-Trp-Ile-Ser-Lys-COOH (SEQ ID NO. 4), peptide comprising the sequence NH.sub.2-Ala-Gln-Leu-Ala-Gly-Glu-Cys-Arg-Glu-Asn-Val-Cys-Met-Gly-Ile-Glu-Gly-Arg-COOH (SEQ ID NO. 3), nucleotide comprising the sequence 5'-CGGACGAATGCTTTGATGTTGTGCTGGACCAGCGTTCATTCTCA-3'(SEQ ID NO.. . .

L12 ANSWER 3 OF 63 USPATFULL
ACCESSION NUMBER: 2002:160542 USPATFULL
TITLE: Method of screening for a modulator of angiogenesis
INVENTOR(S): Lau, Lester F., Chicago, IL, United States
PATENT ASSIGNEE(S): Munin Corporation, Chicago, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 6413735	B1	20020702		
	WO 9733995		19970918		<--
APPLICATION INFO.:	US 1999-142569		19990402	(9)	
	WO 1997-US4193		19970314		
			19990402	PCT 371 date	

NUMBER DATE

PRIORITY INFORMATION:	US 1996-13958P 19960315 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Crouch, Deborah
ASSISTANT EXAMINER:	Woitach, Joseph T.
LEGAL REPRESENTATIVE:	Katten Muchin Zavis
NUMBER OF CLAIMS:	9
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT:	4088

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 6413735 B1 20020702
WO 9733995 19970918 <--

SUMM . . . be induced by a variety of techniques including, but not limited to, the administration of chemicals, e.g., carcinogens, and the **implantation** of cancer cells. A related aspect of the invention is a method for treating a solid tumor comprising the step. . .

SUMM . . . the vascularization of grafts, e.g., skin grafts. Another method of the invention is directed to a process for promoting bone **implantation**, including bone grafts. The method for promoting bone **implantation** comprises the step of contacting a bone implant or receptive site with a biologically effective (i.e., chondrogenically effective) amount of. . . to a biocompatible wrap such as a biodegradable gauze and contacting the wrap with a bone implant, thereby promoting bone **implantation**. The bone implants comprise natural bones and fragments thereof, as well as inanimate natural and synthetic materials that are biocompatible,. . .

DETD . . . cyr61 mRNA expression pattern was determined using an RNase protection technique. O'Brien et al., (1992). In particular, a 289 nucleotide **antisense** riboprobe was used that would protect 246 nucleotides of the murine cyr61 mRNA (nucleotides 67 to 313 using the numbering. . .

DETD . . . according to the manufacturer's instructions. The results showed that cyr61 mRNA is abundant in the human heart, lung, pancreas, and **placenta**; is present at low levels in skeletal muscle, kidney and brain; and is not detectable in liver. These results are. . .

DETD . . . lines 10-29, incorporated herein by reference. A 2.4 kb RNA was identified. The expression of CTGF was high in the **placenta**, lung, heart, kidney, skeletal muscle and pancreas. However, CTGF expression was low in the liver and brain.

DETD . . . Fisp12 was determined. Cyr61 and Fisp12 were co-localized in a number of tissues and organs. A notable example is the **placenta** , where both proteins were readily detectable. In particular, both Cyr61 and Fisp12 were found in and around the trophoblastic giant. . .

DETD In addition to the **placenta**, both Cyr61 and Fisp12 were detected in the cardiovascular system, including the smooth muscle, the cardiomyocytes, and the endothelia. Both. . .

DETD In summary, Cyr61 and Fisp12 have been co-localized in the **placenta** the cardiovascular system, the lung and the skin. Neither protein was detected in the digestive system or the endocrine glands.. . .

DETD . . . described (Polverini, et al., J. Immunol. 118.529-532 [1977]). Sponge implants were evaluated at days 5, 7, 10, and 14 after **implantation**. Thirty minutes before sacrifice, mice were injected with a solution containing [.sup.3H]-thymidine in saline (specific activity 6.7 Ci/mM; New England. . .

DETD . . . vivo, to a sponge laden with Cyr61 in the presence or absence of a suspected modulator of Cyr61 activity. Following **implantation**, incubation, and removal, the relative rates of cell migration are determined. A promoter of Cyr61 activity will increase the rate. . .

DETD To provide slow release of the protein after **implantation** in the cornea, protein is mixed with poly-2-hydroxyethylmethacrylate

(Hydron), or an equivalent agent, to form a pellet of approximately 5. . . made in this way are rehydrated with a drop of sterile lactated Ringers solution and implanted as described above. After **implantation**, the corneal pocket is sealed with erythromycin ointment. After **implantation**, the protein-Hydron pellet should remain near the limbus of the cornea (cornea-sclera border) and vision should not be significantly impaired.

DETD . . . frequently are treated by the introduction of a prosthesis e.g., hip prosthesis, knee prosthesis. Beyond questions of histocompatibility, the successful **implantation** of a prosthetic device requires that the foreign element become integrated into the organism's skeletal structure. The capacity of Cyr61. . . to induce the differentiation of mesenchyme cells into chondrocytes, should prove valuable in the treatment of skeletal disorders by prosthesis **implantation**. For example, integration of a prosthetic device by chondrocyte colonization would be promoted by therapeutic treatments involving the administration of. . .

DETD . . . 179

```
ATG AGC TCC AGC ACC TTC AGG ACG CTC GCT GTC GCC GTC ACC CTT CTC      227
Met Ser Ser Ser Thr Phe Arg Thr Leu Ala Val Ala Val
       Thr Leu Leu
  1               5                  10                  15
CAC TTG ACC AGA CTG GCG CTC TCC ACC TGC CCC GCC GCC TGC CAC TGC      275
His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ala Cys His
       Cys
            20                  25                  30
CCT CTG GAG GCA CCC AAG TGC GCC CCG GGA GTC. . . 50                  55
       60
AGC AAA ACT CAG CCC TGC GAC CAC ACC AAG GGG TTG GAA TGC AAT TTC      419
Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn
       Phe
 65                70                  75                  80
GGC GCC AGC TCC ACC GCT CTG AAA GGG ATC TGC AGA GCT CAG TCA GAA      467
Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu
                  85                  90                  95
GGC AGA CCC TGT GAA TAT AAC. . . AAA CAC CAG TGC ACA TGT ATT GAT GGC GCC GTG
       563
Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val
        115                 120                 125
GGC TGC ATT CCT CTG TGT CCC CAA GAA CTG TCT CTC. . . GAG GTG GAG TTA ACG AGA
       AAC AAT      755
Asp Leu Leu Gly Leu Asp Ala Ser Glu Val Glu Leu Thr Arg Asn Asn
            180                 185                 190
GAG TTA ATC GCA ATT GGA AAA GGC AGC TCA CTG AAG AGG CTT CCT. . . 195
       200                 205
TTT GGC ACC GAA CCG CGA GTT CTT TTC AAC CCT CTG CAC GCC CAT GGC      851
Phe Gly Thr Glu Pro Arg Val Leu Phe Asn Pro Leu His Ala His Gly
    210                 215                 220
CAG AAA TGC ATC GTT CAG ACC ACG TCT TGG TCC CAG TGC TCC AAG AGC      899
Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser Lys
       Ser
225                 230                 235                 240
TGC GGA ACT GGC ATC TCC ACA CGA GTT ACC AAT GAC AAC CCA GAG TGC      947
Cys Gly Thr Gly Ile Ser Thr Arg Val Thr Asn Asp
       Asn Pro Glu Cys
                  245                 250                 255
CGC CTG GTG AAA GAG ACC CGG ATC TGT GAA GTG CGT CCT TGT GGA CAA      995
Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro Cys Gly Gln
            260                 265                 270
CCA GTG TAC AGC AGC CTA AAA AAG. . . AAA TGC AGC AAG ACC AAG      1043
Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys Thr Lys
       275                 280                 285
AAA TCC CCA GAA CCA GTC AGA TTT ACT TAT GCA GGA TGC TCC AGT GTC      1091
Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly Cys Ser Ser Val
    290                 295                 300
```

AAG AAA TAC CGG CCC AAA TAC TGC GGC TCC TGC. . . Cys
305 310 315 320
TGC ACA CCT CTG CAG ACC AGA ACT GTG AAG ATG CGG TTC CGA TGC GAA 1187
Cys **Thr** Pro Leu Gln **Thr** Arg **Thr** Val Lys Met Arg
Phe Arg Cys Glu
325 330 335
GAT GGA GAG ATG TTT TCC AAG AAT GTC ATG. . . CHARACTERISTICS:
LENGTH: 379 amino acids
TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: protein
FEATURE:
NAME/KEY: misc_feature
OTHER INFORMATION: "Mouse Cyr61 amino acid sequence"
SEQUENCE: 2
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Thr Leu Leu
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His Leu **Thr** Arg Leu Ala Leu Ser **Thr** Cys Pro Ala Ala Cys His
Cys
20 25 30
Pro Leu Glu Ala Pro Lys Cys Ala Pro Gly Val. . . 45
Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu Asp Cys
50 55 60
Ser Lys **Thr** Gln Pro Cys Asp His **Thr** Lys Gly Leu Glu Cys Asn
Phe
65 70 75 80
Gly Ala Ser Ser **Thr** Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu
85 90 95
Gly Arg Pro Cys Glu Tyr Asn. . . Ser Arg Ile Tyr Gln Asn Gly Glu Ser
100 105 110
Phe Gln Pro Asn Cys Lys His Gln Cys **Thr** Cys Ile Asp Gly Ala Val
115 120 125
Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu. . . Ser Leu Asp Asp Gln Asp
165 170 175
Asp Leu Leu Gly Leu Asp Ala Ser Glu Val Glu Leu **Thr** Arg Asn Asn
180 185 190
Glu Leu Ile Ala Ile Gly Lys Gly Ser Ser Leu Lys Arg Leu Pro Val
195 200 205
Phe Gly **Thr** Glu Pro Arg Val Leu Phe Asn Pro Leu His Ala His Gly
210 215 220
Gln Lys Cys Ile Val Gln **Thr** **Thr** Ser Trp Ser Gln Cys Ser Lys
Ser
225 230 235 240
Cys Gly **Thr** Gly Ile Ser **Thr** Arg Val **Thr** Asn Asp
Asn Pro Glu Cys
245 250 255
Arg Leu Val Lys Glu **Thr** Arg Ile Cys Glu Val Arg Pro Cys Gly Gln
260 265 270
Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys **Thr** Lys
275 280 285
Lys Ser Pro Glu Pro Val Arg Phe **Thr** Tyr Ala Gly Cys Ser Ser Val
290 295 300
Lys Lys Tyr Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly Arg Cys
305 310 315 320
Cys **Thr** Pro Leu Gln **Thr** Arg **Thr** Val Lys Met Arg
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325 330 335
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168
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His

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      Asn
     65                  70                  75
TTC GGC GCC AGC TCC ACC GCT CTG AAG GGG ATC TGC AGA GCT CAG TCA       408
Phe Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser
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GAG GGC AGA CCC TGT GAA TAT.  .  .  CAA CAT CAG TGC ACA TGT ATT GAT GGC GCC
      504
Ser Phe Gln Pro Asn Cys Gln His Gln Cys Thr Cys Ile Asp Gly Ala
           115                 120                 125
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      GGG CAG TGC TGC GAG      600
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    145                 150                 155
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                 180                 185                 190
TTG ACG AGA AAC AAT GAA TTG ATT GCA GTT GGA AAA GGC AGA TCA CTG       744
Leu Thr Arg Asn Asn Glu Leu Ile Ala Val Gly Lys Gly Arg Ser Leu
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Leu Gln Gly Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln
      Cys
    225                 230                 235
TCA AAG ACC TGT GGA ACT GGT ATC TCC ACA CGA GTT ACC AAT GAC AAC       888
Ser Lys Thr Cys Gly Thr Gly Ile Ser Thr Arg Val
      Thr Asn Asp Asn
240                 245                 250                 255
CCT GAG TGC CGC CTT GTG AAA GAA ACC CGG ATT TGT GAG GTG CGG CCT       936
Pro Glu Cys Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro
                 260                 265                 270
TGT GGA CAG CCA GTG TAC AGC AGC CTG AAA AAG.  .  .  Ser
           275                 280                 285
AAG ACC AAG AAA TCC CCC GAA CCA GTC AGG TTT ACT TAC GCT GGA TGT      1032
Lys Thr Lys Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly
      Cys
       290                 295                 300
TTG AGT GTG AAG AAA TAC CGG CCC AAG TAC TGC GGT TCC TGC.  .  .  315
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Gly Arg Cys Cys Thr Pro Gln Leu Thr Arg Thr Val
      Lys Met Arg Phe
320                 325                 330                 335
CGC TGC GAA GAT GGG GAG ACA TTT TCC AAG AAC GTC ATG ATG ATC CAG      1176
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     50                  55                  60
Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn
      Phe
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Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu
                 85                  90                  95
Gly Arg Pro Cys Glu Tyr Asn.  .  .  Ser Arg Ile Tyr Gln Asn Gly Glu Ser
           100                 105                 110
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145 150 155 160
Trp Val Cys Asp Glu Asp Ser Ile Lys Asp Pro Met. . . 165 170
175
Gly Leu Leu Gly Lys Glu Leu Gly Phe Asp Ala Ser Glu Val Glu Leu
180 185 190
Thr Arg Asn Asn Glu Leu Ile Ala Val Gly Lys Gly Arg Ser Leu Lys
195 200 205
Arg Leu Pro. . . Met Glu Pro Arg Ile Leu Tyr Asn Pro Leu
210 215 220
Gln Gly Gln Lys Cys Ile Val Gln **Thr** **Thr** Ser Trp Ser Gln Cys
Ser
225 230 235 240
Lys **Thr** Cys Gly **Thr** Gly Ile Ser **Thr** Arg Val
Thr Asn Asp Asn Pro
245 250 255
Glu Cys Arg Leu Val Lys Glu **Thr** Arg Ile Cys Glu Val Arg Pro Cys
260 265 270
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275 280 285
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Leu
290 295 300
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305 310 315 320
Arg Cys Cys **Thr** Pro Gln Leu **Thr** Arg **Thr** Val Lys
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325 330 335
Cys Glu Asp Gly Glu **Thr** Phe Ser Lys Asn Val Met Met Ile Gln Ser
340 345 350
Cys Lys Cys Asn Tyr Asn Cys Pro. . . Leu Ala Ser Val Ala Gly Pro Ile Ser Leu
Ala Leu Val Leu Leu
1 5 10 15
Ala Leu Cys **Thr** Arg Pro Ala **Thr** Gly Gln Asp Cys Ser Ala Gln
Cys
20 25 30
Gln Cys Ala Ala Glu Ala Ala Pro His Cys. . . Leu Asp Gly Cys Gly Cys Cys Arg
Val Cys Ala Lys Gln Leu Gly
50 55 60
Glu Leu Cys **Thr** Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu Phe
65 70 75 80
Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys **Thr** Ala
85 90 95
Lys Asp Gly Ala Pro Cys Val Phe Gly Gly Ser Val Tyr Arg Ser Gly
100 105 110
Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys **Thr** Cys Leu Asp Gly
115 120 125
Ala Val Gly Cys Val Pro Leu Cys Ser Met Asp Val Arg Leu. . . Lys Leu Pro Gly
Lys Cys Cys
145 150 155 160
Lys Glu Trp Val Cys Asp Glu Pro Lys Asp Arg **Thr** Ala Val Gly Pro
165 170 175
Ala Leu Ala Ala Tyr Arg Leu Glu Asp **Thr** Phe Gly Pro Asp Pro
Thr
180 185 190
Met Met Arg Ala Asn Cys Leu Val Gln **Thr** **Thr** Glu Trp Ser Ala
Cys
195 200 205
Ser Lys **Thr** Cys Gly Met Gly Ile Ser **Thr** Arg Val **Thr**
Asn Asp Asn
210 215 220

Thr Phe Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg Pro
225 230 235 240
Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys Ile
245 250 255
Arg **Thr** Pro Lys Ile Ala Lys Pro Val Lys Phe Glu Leu Ser Gly Cys
260 265 270
Thr Ser Val Lys **Thr** Tyr Arg Ala Lys Phe Cys Gly Val Cys
Thr Asp
275 280 285
Gly Arg Cys Cys **Thr** Pro His Arg **Thr Thr**
Thr Leu Pro Val Glu Phe
290 295 300
Lys Cys Pro Asp Gly Glu Ile Met Lys Lys Asn Met Met Phe Ile Lys
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Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe Glu
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Ser Leu Tyr. . .
DETD . . . ATGTGGTAGC TCACG 2075
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LENGTH: 349 amino acids
TYPE: amino acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: protein
FEATURE:
NAME/KEY: misc_feature
OTHER INFORMATION: "CTGF amino acid sequence"
SEQUENCE: 8
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50 55 60
Gly Glu Leu Cys **Thr** Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
65 70 75 80
Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys **Thr**
85 90 95
Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly **Thr** Val Tyr Arg Ser
100 105 110
Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys **Thr** Cys Leu Asp
115 120 125
Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu. . . Lys Leu Pro
Gly Lys Cys
145 150 155 160
Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln **Thr** Val Val Gly
165 170 175
Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp **Thr** Phe Gly Pro Asp Pro
180 185 190
Thr Met Ile Arg Ala Asn Cys Leu Val Gln **Thr Thr**
Glu Trp Ser Ala
195 200 205
Cys Ser Lys **Thr** Cys Gly Met Gly Ile Ser **Thr** Arg Val
Thr Asn Asp
210 215 220
Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
225. . . 240
Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
245 250 255
Ile Arg **Thr** Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly
260 265 270
Cys **Thr** Ser Met Lys **Thr** Tyr Arg Ala Lys Phe Cys Gly Val Cys
Thr
275 280 285
Asp Gly Arg Cys Cys **Thr** Pro His Arg **Thr Thr**
Thr Leu Pro Val Glu
290 295 300

Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Asn Met Met Phe Ile
305 310 315 320
Lys **Thr** Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe
325 330 335
Glu Ser Leu Tyr. . . Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu
Asp
1 5 10 15
Cys Ser Lys **Thr** Gln
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LENGTH: 21 amino acids
TYPE: amino acid
STRANDEDNESS: not relevant
TOPOLOGY: not relevant
MOLECULE TYPE: peptide
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Ile Pro Leu Cys Pro
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SEQUENCE CHARACTERISTICS:
LENGTH: 24 amino acids
TYPE: amino acid
STRANDEDNESS: not relevant
TOPOLOGY: not relevant
MOLECULE TYPE: peptide
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Gly
1 5 10 15
Thr Gly Ile Ser **Thr** Arg Val **Thr**
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LENGTH: 26 amino acids
TYPE: amino acid
STRANDEDNESS: not relevant
TOPOLOGY: not relevant
MOLECULE TYPE: peptide
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1 5 10 15
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SEQUENCE CHARACTERISTICS:
LENGTH: 21 amino acids
TYPE: amino acid
STRANDEDNESS: not relevant
TOPOLOGY: not relevant
MOLECULE TYPE: peptide
SEQUENCE: 17
Lys Tyr Cys Gly Ser Cys Val Asp Gly Arg Cys Cys **Thr** Pro Leu Gln
1 5 10 15
Thr Arg **Thr** Val Lys
20

L12 ANSWER 4 OF 63 USPATFULL
ACCESSION NUMBER: 2002:88222 USPATFULL
TITLE: Methods to diagnose a required regulation of trophoblast invasion
INVENTOR(S): Caniggia, Isabella, Toronto, CANADA
Post, Martin, 328 Wellesley Street East, Toronto, CANADA M4X 1H3
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PATENT ASSIGNEE(S): The Hospital for Sick Children (HSC), Toronto, CANADA

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Mount Sinai Hospital Corporation, Toronto, CANADA
(non-U.S. corporation)
Post, Martin, Toronto, CANADA (non-U.S. individual)

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PATENT INFORMATION:	US 6376199	B1	20020423	
	WO 9840747		19980917	<--
APPLICATION INFO.:	US 1999-380662		19991221	(9)
	WO 1998-CA180		19980305	
			19991221	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-39919P	19970307 (60)

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ASSISTANT EXAMINER: Andres, Janet L.
LEGAL REPRESENTATIVE: Merchant & Gould P.C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1,9
NUMBER OF DRAWINGS: 19 Drawing Figure(s); 21 Drawing Page(s)
LINE COUNT: 2297
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6376199 B1 20020423
WO 9840747 19980917 <--

SUMM During placental development the establishment of fetal-maternal interactions is critical for a successful human pregnancy (1). Abnormalities of **placenta** formation due to shallow trophoblast invasion have been linked to preeclampsia and fetal growth restriction (2). In contrast, uncontrolled trophoblast invasion and abnormal trophoblast growth are associated with hydatiform mole and choriocarcinoma. In the course of **placenta** formation, chorionic villous cytotrophoblasts undergo two morphologically distinct pathways of differentiation. The vast majority of cytotrophoblasts in both floating and. . .

SUMM . . . and preterm delivery. There is currently no effective pharmacologic treatment for preeclampsia and the only remedy is to remove the **placenta** (and hence deliver the fetus preterm). Current protocols, including bedrest and antihypertensive drugs, seek to stabilize maternal/fetal condition until delivery. . .

SUMM The present inventors have studied the mechanisms that regulate trophoblast invasion. The inventors have found that **antisense** disruption of the expression of the TGF.beta. receptor, endoglin, triggers invasion of cytotrophoblast from first trimester villous explants in vitro. . . role for TGF-.beta..sub.3 as an endogenous inhibitor of trophoblast invasion. Down-regulation of TGF-.beta..sub.3 (but not .beta..sub.1 or .beta..sub.2) expression using **antisense** oligonucleotides, stimulated extravillous trophoblast cell (EVT) outgrowth/migration and fibronectin production in 5-8 villous explants indicating that TGF-.beta..sub.3 acts to suppress in vivo trophoblast invasion. The effects of **antisense** treatment to TGF-.beta..sub.3 are specific as they are prevented by addition of exogenous TGF-.beta..sub.3 but not TGF-.beta..sub.1 or TGF-.beta..sub.2. The. . .

SUMM . . . the finding that TGF-.beta..sub.3 is highly expressed in trophoblast tissue of preeclamptic patients when compared to that in age-matched control **placenta** while there was no change in the expression of either the .beta..sub.1 or .beta..sub.2 isoform. Fibronectin and .alpha..sub.5 integrin expression were also greater in preeclamptic **placenta**, indicating that in preeclampsia, where there is shallow trophoblast invasion, trophoblast cells are arrested as an .alpha..sub.5 integrin phenotype producing TGF-.beta..sub.3. These

data are supported by the finding that villous explants from a control (non-preeclamptic **placenta**, 32 weeks of gestation) spontaneously formed columns of trophoblasts that invaded the surrounding Matrigel, while explants from a preeclamptic **placenta** did not.

SUMM . . . been found to trigger trophoblast invasion. Follistatin an activin binding protein, inhibited the stimulatory effect of activin, and antibodies and **antisense** to endoglin.

SUMM . . . TGF.beta., but via R-I and R-II they come under the control of this ligand upon entering the decidua. In addition, **antisense** induced disruption of RI (ALK-1) and RII expression stimulated trophoblast outgrowth/migration and fibronectin synthesis. In contrast, **antisense** to RI (ALK-5) inhibited fibronectin synthesis.

DRWD FIG. 3A are Southern blots showing expression of TGF-.beta. isoforms in human **placenta** in the first trimester of gestation:

DRWD FIG. 4A are photographs showing that addition of recombinant TGF.beta..sub.3 to **antisense** TGF.beta..sub.3 abolishes the **antisense** stimulatory effect on trophoblast budding and outgrowth;

DRWD FIG. 4B are blots showing the reversal effect on **antisense** TGF.beta..sub.3 stimulatory effect by exogenous TGF.beta..sub.3 for fibronectin synthesis;

DRWD FIG. 4D are blots showing the effects on gelatinase activity in conditioned media of explants treated with sense or **antisense** oligonucleotides to TGF.beta..sub.3;

DRWD FIG. 4E are blots showing that the **antisense** TGF.beta..sub.3 stimulatory effect on fibronectin production is lost after 9 weeks of gestation:

DRWD FIG. 6A are photographs showing that **antisense** oligonucleotides to TGF.beta..sub.3 induces the formation of trophoblast cells in preeclamptic villous explants;

DRWD FIG. 6B shows the results of gelatin Zymography of explants of 32 weeks gestation from preeclamptic placentae treated with **antisense** or control sense oligonucleotides to TGF.beta..sub.3 for 5 days;

DRWD FIG. 6C are Western blots with MMP9 antisera of explants of 32 weeks gestation from preeclamptic placentae treated with **antisense** or control sense oligonucleotides to TGF.beta..sub.3 for 5 days;

DRWD FIG. 7A is a blot showing expression of HIF-1.alpha. **placenta** in the first trimester of gestation;

DRWD FIG. 7B is a blot showing expression of HIF-1.alpha. in preeclamptic (PE) and age-matched control **placenta** (C);

DRWD FIG. 10 are photographs showing the effect of **antisense** to HIF-1.alpha. on villous explant morphology.

DETD . . . R-II, or RI-RII-endoglin complex) or fragments thereof, may be inverted relative to its normal presentation for transcription to produce an **antisense** nucleic acid molecule. An **antisense** nucleic acid molecule may be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. Examples of **antisense** molecules for TGF.beta..sub.3 are 5'-CCTTTGCAAGTGCATC-3' (SEQ ID NO:1) and 5'-GATGCACTTGCAAAGG-3' (SEQ ID NO:2).

DETD . . . using physical techniques such as microinjection and electroporation or chemical methods such as coprecipitation and incorporation of DNA into liposomes. **Antisense** molecules may also be introduced in vivo using these conventional methods.

DETD Villous explants kept in culture for 6 days in the presence or absence of **antisense** oligonucleotides to endoglin were dissected away from the insert membrane with the supporting Matrigel. Explants and placental tissue of 9. . .

DETD **Antisense** Oligonucleotides and Their Effects on EVT Formation

DETD . . . against sequences adjacent to the AUG initiation codon of human endoglin (23) mRNA were synthesized. Previous studies have demonstrated that **antisense** oligonucleotides, targeted to sequences adjacent to initiation codons, are most efficient in inhibiting translation (24). Furthermore, 16-mer oligonucleotides are short. . .

be taken up efficiently and provide sufficient specificity for hybridization to the corresponding target mRNA (24). The sequences of the **antisense** and sense endoglin oligonucleotides were 5'-GCGTGCCGCGGTCCAT-3' (SEQ ID NO:3) and 5'-ATGGACCGCGGCACGC-3' (SEQ ID NO:4), respectively. An oligomer with the same composition as the **antisense** oligonucleotide, but with a scrambled sequence, 5'-GCGGGCCTCGTTCCAG-3' (SEQ ID NO:5), was also synthesized and used as a negative control. Oligonucleotides were dissolved in water and their concentration was estimated by optical density at OD.sub.260. **Antisense** or sense oligonucleotides (5-10 .mu.M) were added to the villous explants on day 1 and day 3 of culture. EVT. . .

DETD . . . DMEM/F12. Explants were then washed and incubated in DMEM/F12 containing either 10 .mu.g/ml MAb 44G4 or non-immune IgG, 10 .mu.M **antisense**, scrambled or sense endoglin oligonucleotides. The medium with or without the various agents was changed on day 3 and was. . .

DETD Villous explants of 5-8 weeks gestation, cultured for 48 h with and without **antisense** ON to endoglin, were incubated in the presence of 1 .mu.Ci of [.sup.3H]thymidine per milliliter of medium. After 6 h. . .

DETD Stimulation of EVT Outgrowth and Migration by Antibody and **Antisense** Oligonucleotides to Endoglin

DETD **Antisense** endoglin also enhanced the number of EVT outgrowths as well as their migration and invasion into the Matrigel. Control explants,. . .

DETD The stimulatory effect of **antisense** endoglin oligonucleotides on EVT outgrowth and migration was observed on day 3 of culture with 6.87.+-.1.5 in the **antisense**-treated group versus 1.42.+-.0.41 in the sense-treated group ($p<0.05$). After 5 days of exposure, the number of EVT/villous tip increased from 2.08.+-.0.47 in sense-treated explants to 8.46.+-.1.7 in **antisense**-treated cultures. The **antisense**-endoglin effect on trophoblast differentiation was specific as incubation of explants with an equivalent amount of either sense endoglin or scrambled **antisense**-endoglin oligonucleotide (not shown) had no effect. **Antisense** endoglin stimulated EVT outgrowth and migration in a concentration-dependent manner with maximal stimulation observed at 10 .mu.M.

DETD . . . undergo proliferation (21), whereas differentiated EVT do not. Therefore, studies were carried out to determine if EVT outgrowth triggered by **antisense** endoglin treatment was due to cell division or migration. [.sup.3H]Thymidine autoradiography of explants exposed to **antisense** endoglin ON showed villous trophoblast proliferation within the villous tip at the proximal site of the forming column, while both. . .

DETD . . . repertoire (4). When placental explants of 5-8 weeks gestation were maintained in culture for 5 days in the presence of **antisense**-endoglin oligonucleotides, the stimulation of EVT outgrowth and migration was also accompanied by changes in integrin expression. The .alpha..sub.6 integrin subunit. . .

DETD . . . EVT outgrowth is observed under basal culture conditions, the expression of endoglin in trophoblast columns could only be studied in **antisense**-treated explants. Immunohistochemical analysis of explants treated with **antisense** oligonucleotides to endoglin revealed that in intact villi the syncytiophoblast maintained high levels of endoglin. Low levels of endoglin and. . . appears non-specific as it was also observed with non-immune IgG. The staining of endoglin in EVT of explants treated with **antisense** endoglin was weakly positive when compared to sections of the same explant stained with control IgG. In addition, endoglin expression in proximal columns of explants was much reduced when compared to sections of 9 weeks gestation **placenta** stained under similar conditions. When a subsequent section of this **placenta** is stained for .alpha..sub.5 integrin, the transition zone in the proximal column is clearly visualized as negative for .alpha..sub.5, but positive for endoglin. The .alpha..sub.5 integrin in explants treated with

antisense endoglin was also found to be highly expressed in EVT within proximal and distal columns. These data suggest that **antisense** endoglin treatment, which promotes EVT outgrowth and migration in explant cultures, induces a decrease in endoglin expression at the level. . .

DETD . . . the anchoring villi and its production is increased during EVT differentiation (27). Thus the effect of either 44G4 IgG or **antisense** endoglin on fibronectin synthesis by villous explants from 5-8 weeks gestation was investigated. Explants were metabolically labelled on day 4. . . and newly synthesized FN released into the media over a period of 18 h was measured. Both 44G4 IgG and **antisense**-endoglin oligonucleotides induced a significantly greater production of FN than that observed in control IgG or sense oligonucleotide-treated cultures. PhosphoImager analysis. . . a 8- and 5-fold increase in FN synthesis (5 independent experiments carried out in triplicate, $p<0.05$) for 44G4 IgG and **antisense**-endoglin treated explants, respectively, relative to control sense or DMEM/F12 alone. FN production in villous explants, cultured in the presence of a scrambled **antisense** endoglin oligonucleotide, was similar to that observed in sense-treated explants or in medium alone.

DETD . . . essential component of the receptor complex in mediating the effects of TGF-.beta..sub.1 and TGF-.beta..sub.3, villous explants were preincubated with either **antisense** or antibody to endoglin to trigger EVT differentiation. After an overnight incubation, exogenous TGF-.beta..sub.1, TGF-.beta..sub.2 or TGF-.beta..sub.3 were added at. . . were metabolically labelled at day 5 of culture and FN synthesis was measured. PhosphoImager analysis demonstrated that both antibody and **antisense** to endoglin significantly stimulated FN synthesis. Addition of exogenous TGF-.beta..sub.1 and TGF-.beta..sub.3 to explant cultures incubated with **antisense** ON or antibody to endoglin, which binds both isoforms, did not alter the stimulatory effect of **antisense** ON and antibody to endoglin on FN synthesis. In contrast, addition of TGF-.beta..sub.2, which does not interact with endoglin, overcame the antibody and **antisense** ON stimulatory effect on FN synthesis. TGF-.beta..sub.2, but not -.beta..sub.1 and -.beta..sub.3, inhibited also the EVT outgrowth and migration induced by the **antisense** endoglin treatment.

DETD Treatment of human villous explants from 5-8 weeks gestation with antibodies and **antisense** oligonucleotides to endoglin stimulated EVT differentiation along the invasive pathway. This was manifested by 1) a significant increase in EVT. . .

DETD . . . endoglin may contribute to the major complications of pregnancy such as preeclampsia or choriocarcinoma, associated with abnormal trophoblast invasion and **placenta** development.

DETD . . . with an upregulation of fibronectin synthesis and integrin switching. Trophoblast invasion at 5-7 weeks can be induced by incubation with **antisense** to TGF-.beta..sub.3, TGF.beta. receptor I (ALK-1) or TGF.beta. receptor II. Only minimal invasion occurred in response to **antisense** to TGF.beta..sub.1 and **antisense** TGF.beta..sub.2 failed to induce invasion. These data suggest that TGF-.beta..sub.3 via the ALK-1-receptor II complex is a major regulator of. . .

DETD Total RNA was extracted from the **placenta**, reverse transcribed and amplified by 15 cycles of PCR using TGF.beta. isoform specific primers. RT-PCR products were analysed by Southern. . .

DETD Villous explant cultures were established as described previously (I. Caniggia et al. Endocrinology, 138, 3976 1997, O. Genbacev et al., **Placenta** 13:439, 1992) from first trimester human placentae (5-10 weeks gestation) or from preeclamptic and age-matched control placentae (30 and 32. . . (L. Chesley, Obstet. Gynecol. 65, 423, 1985). Following an overnight period in serum-free DMEM/F12, explants were cultured in media containing **antisense** or sense oligonucleotides (10 .mu.M) for up to 6 days (with changes of media/oligonucleotides every 48 hours). Phosphorothioate oligonucleotides of. . .

DETD . . . W. K. Ritchie, S. J. Lye, M. Letarte, Endocrinology, 138, 4977 (1997), O. Genbacev, S. A. Schubach, R. K. Miller, **Placenta** 13, 439, (1992)). Morphologic (EVT outgrowth) and biochemical (fibronectin [FN] synthesis and gelatinase activity) indices of trophoblast invasion were monitored in response to **antisense** (AS) induced suppression of TGF.beta. isoform expression in explants at 5-8 weeks of gestation. Explants exposed to AS TGF.beta..sub.3 (but. . .

DETD . . . .alpha..sub.5 and fail to express .alpha..sub.1 were also obverved in preeclamptic placentae. These data suggest that the trophoblasts from preeclamptic **placenta** are arrested at a relatively immature phenotype possibly due to a failure to undergo complete differentiation along the invasive pathway. . .

DETD . . . here demonstrate not only that abnormalities in TGF.beta..sub.3 expression are associated with preeclampsia but also that down-regulation of TGF.beta..sub.3 with **antisense** oligonucleotides restores the invasive capability of preeclamptic trophoblasts. The data are consistent with a model of normal placentation in which. . . contributes to the remodelling of the uterine spiral arteries and ultimately enables the establishment of increased vascular perfusion of the **placenta**. In placentae predisposed to preeclampsia, TGF.beta..sub.3 expression remains abnormally elevated and trophoblasts remain in a relatively immature state of differentiation.. . .

DETD . . . FIG. 9 showing the effect of low oxygen tension on villous explant morphology; and FIG. 10 showing the effect of **antisense** to HIF-1.alpha. on villous explant morphology.

DETD . . . TGF.beta..sub.3, R-I is expressed at greater levels in trophoblast tissue of preeclamptic patients when compared to that in age-matched control **placenta**. **Antisense** disruption of R-I (ALK-1) and R-II expression stimulated trophoblast outgrowth/migration and FN synthesis. In contrast, **antisense** to R-I (ALK-5) inhibited FN synthesis.

DETD 1. Cross J C, Werb Z, Fisher, S J, 1994. **Implantation** and the **placenta**: key pieces of the development puzzle. Science, 266:1508-1518.

DETD 3. Aplin J D, 1991. **Implantation**, trophoblast differentiation and haemochorial placentation: mechanistic evidence in vivo and in vitro. J. Cell Science, 99: 681-692.

DETD . . . Lye S J, Letarte M, 1994. Localization of endoglin, a transforming growth-factor-b binding protein, and of CD44 and integrins in **placenta** during the first trimester of pregnancy. Biol Reprod. 51: 405-413.

DETD . . . J A, Lala P K, 1995. Localization of transforming growth factor b and its natural inhibitor decorin in the human **placenta** and decidua throughout gestation. **Placenta**, 16: 221-231.

DETD . . . I and type II transforming growth factor-b (TGF-b) receptors with different affinities for TGF-b1 and TGF-b2 are exhibited by human **placenta** trophoblasts. J. Cell. Physiol. 150: 334-343.

DETD 21. Genbacev O, Schubach S A, Miller R K, (1992). Villous culture of first trimester human **placenta**-Model to study extravillous trophoblast (EVT) differentiation. **Placenta**, 13: 439-461.

DETD 24. Malcolm A D B, 1992. Uses and applications of **antisense** oligonucleotides: uses of **antisense** nucleic acids-an introduction. Bioch. Soc. Trans. 20: 745-746.

DETD 27. Feinberg R F, Kilman H J, Locwood C J, 1991 Is oncofetal fibronectin a trophoblast glue for human **implantation**? Am. J. Pathol. 138: 537-543.

DETD . . . C J, Aplin J D, 1995. Trophoblast differentiation during formation of anchoring villi in a model of the early human **placenta** in vitro. **Placenta**, 16: 41-56.

DETD . . . F, Kliman H J, Wang C-L, 1994. Transforming growth factor-b stimulates trophoblast oncofetal fibronectin synthesis in vitro: implications for trophoblast **implantation** in vivo. J.Clin. Endocrinol Metab. 78: 1241-1248.

DETD Expression of TGF-.beta. isoforms in human **placenta** in the first trimester of gestation. (FIG. 3A) Message expression of TGF.beta. isoforms was assessed by low cycle RT-PCR followed. . . column (EVT, thin arrow) but was absent in the transitional zone where polarized cells become unpolarized (thick arrows). Sections of **placenta** at 12 weeks gestation demonstrate low or absent TGF-.beta..sub.3 immunoreactivity in the villi. There is no immunoreactivity when antiserum was. . .

DETD **Antisense** TGF.beta..sub.3 stimulates trophoblast migration, fibronectin production and gelatinase, activity. Explants of 5-8 weeks gestation were treated for 5 days with 10 .mu.M **antisense** oligonucleotides to TGF.beta..sub.3 (AS-.beta.3), AS-.beta.3 plus 10 ng/ml recombinant TGF.beta..sub.3 (AS-.beta.3+.beta.3) or AS-.beta.3 plus recombinant TGF.beta.1 (AS-.beta.3+.beta.1). Control experiments were. . . (S-.beta.3) or medium alone (FIG. 4C). (FIG. 4A) Shown is a representative experiment demonstrating that addition of recombinant TGF.beta..sub.3 to **antisense** TGF.beta..sub.3 treated explants (AS-.beta.3+.beta.3) abolishes the **antisense** stimulatory effect on trophoblasts budding and outgrowth (arrows). (FIG. 4B) Similar reversal effect on AS-.beta.3 stimulatory effect by exogenous TGF.beta..sub.3. . . 4-6. AS-.beta.3 treated explants; lanes 7-9, AS-.beta.3+.beta.3 treated explants. (FIG. 4C) Changes in fibronectin estimated after normalization to control cultures. **Antisense** TGF.beta..sub.3 treatment (AS-.beta.3, solid bar) significantly incresed ($p<0.05$; one-way ANOVA followed by Student-Newman-Keuls test for non-paired groups) the amount of. . . sense (S-.beta.3, cross bar). Addition of exogenous TGF.beta..sub.3 (AS-.beta.3+.beta.3 squares bar) but not TGF.beta..sub.1 (AS-.beta.3+.beta.1 cross hatched bar) to the **antisense** treated explants abolished the **antisense** stimulatory effect on fibronectin production, demonstrating the specificity of the action of TGF.beta..sub.3. (FIG. 4D) Getatinase activity in conditioned media of explants treated with sense or **antisense** oligonucleotides to TGF.beta.3. Arrows indicate positions of getatinases activity (MMP2: 60, 68; MMP9: 84 and 92, kDa). (FIG. 4E) The **antisense** TGF.beta..sub.3 stimulatory effect on fibronectin production is lost after 9 weeks of gestation. Explants of 6 and 10 weeks gestation were treated with 10 .mu.M **antisense** (AS-.beta.3) or control sense (S-.beta.3) oligonucleotides to TGF.beta..sub.3. Newly synthesized fibronectin was isolated from the medium as described above. Representative. . .

DETD **Antisense** oligonucleotides to TGF.beta..sub.3 induces the formation of columns of trophoblast cells in preeclamptic villous explants. Villous explant cultures were prepared from preeclamnptic and age-matched control placentae. Explants were maintained in culture in the presence of either control sense or **antisense** oligonucleotides to TGF.beta..sub.3 for 5 days. Morphological integrity was recoded daily. Explants from normal **placenta** (32 weeks), exposed to sense oligonucleotides (S-.beta.3) spontaneously form columns of trophoblast cells which migrate and invade into the surrounding Matrigel (arrows), while explants from preeclamptic **placenta** (32 weeks) exposed to sense oligonucleotides do not. In contrast, **antisense** treatment (AS-.beta.3) triggers the formation of invading trophoblast columns (arrows) in preeclamptic placentae.

DETD **Antisense** oligonucleotides to TGF.beta..sub.3 triggers gelatinase activity and expression in preeclamptic villous explants. Explants of 32 weeks gestation from preeclamptic placentae were treated with **antisense** (AS-.beta.3) or control sense (S-.beta.3) oligonucleotides to TGF.beta..sub.3 for 5 days. Samples of conditioned medium were collected at day 5. . .

DETD . . . ctg aac ttt gcc acg gtc agc ctc tct ctg tcc act tgc acc
337
Ala Leu Leu Asn Phe Ala **Thr** Val Ser Leu Ser Leu Ser **Thr** Cys
Thr
15 20 25
acc ttg gac ttc ggc cac atc aag aag aag agg gtg gaa gcc att agg 385

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  Thr Leu Asp Phe Gly His Ile Lys Lys Lys Arg Val Glu Ala Ile Arg
    30                  35                  40
gga cag atc.  .  .  aag ctc agg ctc acc agc ccc cct gag cca acg      433
Gly Gln Ile Leu Ser Lys Leu Arg Leu Thr Ser Pro Pro Glu Pro
       Thr
45                  50                  55                  60
gtg atg acc cac gtc ccc tat cag gtc ctg gcc ctt tac aac agc acc      481
Val Met Thr His Val Pro Tyr Gln Val Leu Ala Leu Tyr Asn Ser
       Thr
                65                  70                  75
cgg gag ctg ctg gag gag atg cat ggg gag agg gag gaa ggc tgc acc      529
Arg Glu Leu Leu Glu Glu Met His Gly Glu Arg Glu Glu Gly Cys Thr
            80                  85                  90
cag gaa aac acc gag tcg gaa tac tat gcc aaa gaa atc cat aaa ttc      577
Gln Glu Asn Thr Glu Ser Glu Tyr Tyr Ala Lys Glu Ile His Lys Phe
        95                  100                 105
gac atg atc cag ggg ctg.  .  .  115                 120
aaa gga att acc tcc aag gtt ttc cgc ttc aat gtg tcc tca gtg gag      673
Lys Gly Ile Thr Ser Lys Val Phe Arg Phe Asn Val Ser Ser Val Glu
125                 130                 135                 140
aaa aat aga acc aac cta ttc cga gca gaa ttc cgg gtc ttg cgg gtg      721
Lys Asn Arg Thr Asn Leu Phe Arg Ala Glu Phe Arg Val Leu Arg Val
                145                 150                 155
ccc aac ccc agc tct aag.  .  .  185
aag aat ctg ccc aca cgg ggc act gcc gag tgg ctg tcc ttt gat gtc      865
Lys Asn Leu Pro Thr Arg Gly Thr Ala Glu Trp Leu Ser Phe Asp
       Val
    190                 195                 200
act gac act gtg cgt gag tgg ctg ttg aga aga gag tcc aac tta ggt      913
  Thr Asp Thr Val Arg Glu Trp Leu Leu Arg Arg Glu Ser Asn Leu
       Gly
205                 210                 215                 220
cta gaa atc agc att.  .  .  tgt cca tgt cac acc ttt cag ccc aat gga      961
Leu Glu Ile Ser Ile His Cys Pro Cys His Thr Phe Gln Pro Asn Gly
                225                 230                 235
gat atc ctg gaa aac att cac gag gtg atg gaa atc aaa.  .  .  295
       300
gct ttg gac acc aat tac tgc ttc cgc aac ttg gag gag aac tgc tgt     1201
Ala Leu Asp Thr Asn Tyr Cys Phe Arg Asn Leu Glu Glu Asn Cys Cys
                305                 310                 315
gtg cgc ccc ctc tac att.  .  .  cgc agt gca gac aca acc cac agc acg gtg ctg gga
       ctg    1345
Pro Tyr Leu Arg Ser Ala Asp Thr Thr His Ser Thr
       Val Leu Gly Leu
    350                 355                 360
tac aac act ctg aac cct gaa gca tct gcc tcg cct tgc tgc gtg ccc     1393
Tyr Asn Thr Leu Asn Pro Glu Ala Ser Ala Ser Pro Cys Cys Val Pro
365                 370                 375                 380
cag gac ctg gag ccc ctg acc atc ctg tac tat gtt ggg agg acc ccc     1441
Gln Asp Leu Glu Pro Leu Thr Ile Leu Tyr Tyr Val Gly Arg Thr
       Pro
                385                 390                 395
aaa gtg gag cag ctc tcc aac atg gtg gtg aag tct tgt aaa tgt agc     1489
Lys.  .  .  21
Met Lys Met His Leu Gln Arg Ala Leu Val Val Leu Ala Leu Leu Asn
1               5                   10                  15
Phe Ala Thr Val Ser Leu Ser Leu Ser Thr Cys Thr
       Thr Leu Asp Phe
            20                  25                  30
Gly His Ile Lys Lys Lys Arg Val Glu Ala Ile Arg Gly Gln Ile Leu
        35                  40                  45
Ser Lys Leu Arg Leu Thr Ser Pro Pro Glu Pro Thr Val Met
       Thr His
    50                  55                  60
Val Pro Tyr Gln Val Leu Ala Leu Tyr Asn Ser Thr Arg Glu Leu Leu
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65                  70                  75                  80
Glu Glu Met His Gly Glu Arg Glu Glu Gly Cys Thr Gln Glu Asn
       Thr
                85                  90                  95
Glu Ser Glu Tyr Tyr Ala Lys Glu Ile His Lys Phe Asp Met Ile Gln
            100                 105                 110
Gly Leu Ala Glu His Asn Glu Leu Ala Val Cys Pro Lys Gly Ile Thr
        115                 120                 125
Ser Lys Val Phe Arg Phe Asn Val Ser Ser Val Glu Lys Asn Arg Thr
    130                 135                 140
Asn Leu Phe Arg Ala Glu Phe Arg Val Leu Arg Val Pro Asn Pro Ser
145                 150                 155.  .  .  165                 170
       175
Asp Glu His Ile Ala Lys Gln Arg Tyr Ile Gly Gly Lys Asn Leu Pro
            180                 185                 190
  Thr Arg Gly Thr Ala Glu Trp Leu Ser Phe Asp Val Thr
       Asp Thr Val
        195                 200                 205
Arg Glu Trp Leu Leu Arg Arg Glu Ser Asn Leu Gly Leu Glu Ile Ser
    210                 215                 220
Ile His Cys Pro Cys His Thr Phe Gln Pro Asn Gly Asp Ile Leu Glu
225                 230                 235                 240
Asn Ile His Glu Val Met Glu Ile Lys.  .  .  His Arg Leu
        275                 280                 285
Asp Asn Pro Gly Gln Gly Gly Gln Arg Lys Lys Arg Ala Leu Asp Thr
    290                 295                 300
Asn Tyr Cys Phe Arg Asn Leu Glu Glu Asn Cys Cys Val Arg Pro Leu
305                 310                 315.  .  .  Gly Tyr Tyr Ala Asn Phe Cys
       Ser Gly Pro Cys Pro Tyr Leu Arg
            340                 345                 350
Ser Ala Asp Thr Thr His Ser Thr Val Leu Gly Leu
       Tyr Asn Thr Leu
        355                 360                 365
Asn Pro Glu Ala Ser Ala Ser Pro Cys Cys Val Pro Gln Asp Leu Glu
    370                 375                 380
Pro Leu Thr Ile Leu Tyr Tyr Val Gly Arg Thr Pro Lys Val Glu
       Gln
385                 390                 395                 400
Leu Ser Asn Met Val Val Lys Ser Cys Lys Cys Ser
                405.  .  .  gtg atg agg ctt acc atc agc tat ttg cgt gtg agg aaa
       ctt      244
Ala Ser Val Met Arg Leu Thr Ile Ser Tyr Leu Arg Val Arg Lys Leu
            60                  65                  70
ctg gat gct ggt gat ttg gat att gaa.  .  .  gtt atg gtt ctc aca      340
Asn Cys Phe Tyr Leu Lys Ala Leu Asp Gly Phe Val Met Val Leu Thr
    90                  95                  100
gat gat ggt gac atg att tac att tct gat aat gtg aac aaa tac atg      388
Asp Asp.  .  .  110                 115                 120
gga tta act cag ttt gaa cta act gga cac agt gtg ttt gat ttt act      436
Gly Leu Thr Gln Phe Glu Leu Thr Gly His Ser Val Phe Asp Phe
       Thr
                125                 130                 135
cat cca tgt gac cat gag gaa atg aga gaa atg ctt aca cac aga aat      484
His Pro Cys Asp His Glu Glu Met Arg Glu Met Leu Thr His Arg Asn
            140                 145                 150
ggc ctt gtg aaa aag ggt aaa gaa caa aac aca cag cga agc ttt ttt      532
Gly Leu Val Lys Lys Gly Lys Glu Gln Asn Thr Gln Arg Ser Phe Phe
        155                 160                 165
ctc aga atg aag tgt acc cta act agc cga gga aga act atg aac ata      580
Leu Arg Met Lys Cys Thr Leu Thr Ser Arg Gly Arg Thr
       Met Asn Ile
    170                 175                 180
aag tct gca aca tgg aag gta ttg cac tgc aca ggc cac att cac gta      628
Lys Ser Ala Thr Trp Lys Val Leu His Cys Thr Gly His Ile His
       Val
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185 190 195 200
tat gat acc aac agt aac caa cct cag tgt ggg tat aag aaa cca cct 676
Tyr Asp **Thr** Asn Ser Asn Gln Pro Gln Cys Gly Tyr Lys Lys Pro Pro
205 210 215
atg acc tgc ttg gtg ctg att tgt gaa ccc att cct cac cca tca aat 724
Met **Thr** Cys Leu Val Leu Ile Cys Glu Pro Ile Pro His Pro Ser Asn
220 225 230
att gaa att cct. . . tta gat agc aag act ttc ctc agt cga cac agc ctg
772
Ile Glu Ile Pro Leu Asp Ser Lys **Thr** Phe Leu Ser Arg His Ser Leu
235 240 245
gat atg aaa ttt tct tat tgt gat gaa aga att acc gaa ttg atg gga 820
Asp Met Lys Phe Ser Tyr Cys Asp Glu Arg Ile **Thr** Glu Leu Met Gly
250 255 260
tat gag cca gaa gaa ctt tta ggc cgc tca att tat gaa tat. . . tct gat cat ctg
acc aaa act cat cat gat atg ttt act 916
Ala Leu Asp Ser Asp His Leu **Thr** Lys **Thr** His His Asp Met Phe
Thr
285 290 295
aaa gga caa gtc acc aca gga cag tac agg atg ctt gcc aaa aga ggt 964
Lys Gly Gln Val **Thr** **Thr** Gly Gln Tyr Arg Met Leu Ala Lys Arg
Gly
300 305 310
gga tat gtc tgg gtt gaa act caa gca act gtc ata tat aac acc aag 1012
Gly Tyr Val Trp Val Glu **Thr** Gln Ala **Thr** Val Ile Tyr Asn
Thr Lys
315 320 325
aat tct caa cca cag tgc att gta tgt gtg aat tac gtt gtg agt ggt 1060
Asn. . . tcc ctt caa caa aca gaa tgt gtc 1108
Ile Ile Gln His Asp Leu Ile Phe Ser Leu Gln Gln **Thr** Glu Cys Val
345 350 355 360
ctt aaa ccg gtt gaa tct tca gat atg aaa atg act cag cta ttc acc 1156
Leu Lys Pro Val Glu Ser Ser Asp Met Lys Met **Thr** Gln Leu Phe
Thr
365 370 375
aaa gtt gaa tca gaa gat aca agt agc ctc ttt gac aaa ctt aag aag 1204
Lys Val Glu Ser Glu Asp **Thr** Ser Ser Leu Phe Asp Lys Leu Lys Lys
380 385 390
gaa cct gat gct tta act ttg ctg gcc cca gcc gct gga gac aca atc 1252
Glu Pro Asp Ala Leu **Thr** Leu Leu Ala Pro Ala Ala Gly Asp **Thr**
Ile
395 400 405
ata tct tta gat ttt ggc agc aac gac aca gaa act gat gac cag caa 1300
Ile Ser Leu Asp Phe Gly Ser Asn Asp **Thr** Glu **Thr** Asp Asp Gln
Gln
410 415 420
ctt gag gaa gta cca tta tat aat gat gta atg ctc ccc tca. . . tct cca tta ccc
acc gct 1396
Glu Lys Leu Gln Asn Ile Asn Leu Ala Met Ser Pro Leu Pro **Thr** Ala
445 450 455
gaa acg cca aag cca ctt cga agt agt gct gac cct gca ctc aat caa 1444
Glu **Thr** Pro Lys Pro Leu Arg Ser Ser Ala Asp Pro Ala Leu Asn Gln
460 465 470
gaa gtt gca tta. . . Ser
475 480 485
ttt acc atg ccc cag att cag gat cag aca cct agt cct tcc gat gga 1540
Phe **Thr** Met Pro Gln Ile Gln Asp Gln **Thr** Pro Ser Pro Ser Asp
Gly
490 495 500
agc act aga caa agt tca cct gag cct aat agt ccc agt gaa tat tgt 1588
Ser **Thr** Arg Gln Ser Ser Pro Glu Pro Asn Ser Pro Ser Glu Tyr Cys
505 510 515 520
ttt tat gtg gat. . . ttt gct gaa gac aca gaa gca aag aac cca ttt tct act
1684
Glu Lys Leu Phe Ala Glu Asp **Thr** Glu Ala Lys Asn Pro Phe Ser

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       Thr
            540                 545                 550
cag gac aca gat tta gac ttg gag atg tta gct ccc tat atc cca atg     1732
Gln Asp Thr Asp Leu Asp Leu Glu Met Leu Ala Pro Tyr Ile Pro Met
        555                 560                 565
gat gat gac ttc cag.  .  .  agt cct caa agc aca gtt aca     1828
Ser Ser Ser Ala Ser Pro Glu Ser Ala Ser Pro Gln Ser Thr Val
       Thr
585                 590                 595                 600
gta ttc cag cag act caa ata caa gaa cct act gct aat gcc acc act     1876
Val Phe Gln Gln Thr Gln Ile Gln Glu Pro Thr Ala Asn Ala
       Thr Thr
                605                 610                 615
acc act gcc acc act gat gaa tta aaa aca gtg aca aaa gac cgt atg     1924
  Thr Thr Ala Thr Thr Asp Glu Leu Lys
       Thr Val Thr Lys Asp Arg Met
            620                 625                 630
gaa gac att aaa ata ttg att gca tct cca tct cct acc cac ata cat     1972
Glu Asp Ile Lys Ile Leu Ile Ala Ser Pro Ser Pro Thr His Ile His
        635                 640                 645
aaa gaa act act agt gcc aca tca tca cca tat aga gat act caa agt     2020
Lys Glu Thr Thr Ser Ala Thr Ser Ser Pro Tyr Arg
       Asp Thr Gln Ser
    650                 655                 660
cgg aca gcc tca cca aac aga gca gga aaa gga gtc ata gaa cag aca     2068
Arg Thr Ala Ser Pro Asn Arg Ala Gly Lys Gly Val Ile Glu Gln
       Thr
665                 670                 675                 680
gaa aaa tct cat cca aga agc cct aac gtg tta tct gtc gct ttg agt     2116
Glu Lys.  .  .  685                 690                 695
caa aga act aca gtt cct gag gaa gaa cta aat cca aag ata cta gct     2164
Gln Arg Thr Thr Val Pro Glu Glu Glu Leu Asn Pro Lys Ile Leu
       Ala
            700                 705                 710
ttg cag aat gct cag aga.  .  .  gta gga att gga aca tta tta cag cag cca gac gat
       cat     2260
Phe Gln Ala Val Gly Ile Gly Thr Leu Leu Gln Gln Pro Asp Asp His
    730                 735                 740
gca gct act aca tca ctt tct tgg aaa cgt gta aaa gga tgc aaa tct     2308
Ala Ala Thr Thr Ser Leu Ser Trp Lys Arg Val Lys Gly Cys Lys Ser
       Ser
745                 750                 755                 760
agt gaa cag aat gga atg gag caa aag aca att att tta ata ccc tct     2356
Ser Glu Gln Asn Gly Met Glu Gln Lys Thr Ile Ile Leu Ile Pro Ser
                765                 770                 775
gat tta gca tgt aga ctg ctg ggg caa tca atg gat.  .  .  785                 790
cca cag ctg acc agt tat gat tgt gaa gtt aat gct cct ata caa ggc     2452
Pro Gln Leu Thr Ser Tyr Asp Cys Glu Val Asn Ala Pro Ile Gln Gly
        795                 800                 805
agc aga aac cta ctg cag.  .  .
DETD   .  .  .  Pro Leu Pro His
        35                  40                  45
Asn Val Ser Ser His Leu Asp Lys Ala Ser Val Met Arg Leu Thr Ile
    50                  55                  60
Ser Tyr Leu Arg Val Arg Lys Leu Leu Asp Ala Gly Asp Leu Asp Ile
65                  70.  .  .  Ala Gln Met Asn Cys Phe Tyr Leu Lys Ala Leu
                85                  90                  95
Asp Gly Phe Val Met Val Leu Thr Asp Asp Gly Asp Met Ile Tyr Ile
            100                 105                 110
Ser Asp Asn Val Asn Lys Tyr Met Gly Leu Thr Gln Phe Glu Leu
       Thr
        115                 120                 125
Gly His Ser Val Phe Asp Phe Thr His Pro Cys Asp His Glu Glu Met
    130                 135                 140
Arg Glu Met Leu Thr His Arg Asn Gly Leu Val Lys Lys Gly Lys Glu
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145 150 155 160
Gln Asn **Thr** Gln Arg Ser Phe Phe Leu Arg Met Lys Cys **Thr** Leu
Thr
165 170 175
Ser Arg Gly Arg **Thr** Met Asn Ile Lys Ser Ala **Thr** Trp Lys Val
Leu
180 185 190
His Cys **Thr** Gly His Ile His Val Tyr Asp **Thr** Asn Ser Asn Gln
Pro
195 200 205
Gln Cys Gly Tyr Lys Lys Pro Pro Met **Thr** Cys Leu Val Leu Ile Cys
210 215 220
Glu Pro Ile Pro His Pro Ser Asn Ile Glu Ile Pro Leu Asp Ser Lys
225 230 235 240
Thr Phe Leu Ser Arg His Ser Leu Asp Met Lys Phe Ser Tyr Cys Asp
245 250 255
Glu Arg Ile **Thr** Glu Leu Met Gly Tyr Glu Pro Glu Glu Leu Leu Gly
260 265 270
Arg Ser Ile Tyr Glu Tyr Tyr His Ala Leu Asp Ser Asp His Leu **Thr**
275 280 285
Lys **Thr** His His Asp Met Phe **Thr** Lys Gly Gln Val **Thr**
Thr Gly Gln
290 295 300
Tyr Arg Met Leu Ala Lys Arg Gly Gly Tyr Val Trp Val Glu **Thr** Gln
305 310 315 320
Ala **Thr** Val Ile Tyr Asn **Thr** Lys Asn Ser Gln Pro Gln Cys Ile
Val
325 330 335
Cys Val Asn Tyr Val Val Ser Gly Ile Ile Gln His Asp Leu Ile Phe
340 345 350
Ser Leu Gln Gln **Thr** Glu Cys Val Leu Lys Pro Val Glu Ser Ser Asp
355 360 365
Met Lys Met **Thr** Gln Leu Phe **Thr** Lys Val Glu Ser Glu Asp
Thr Ser
370 375 380
Ser Leu Phe Asp Lys Leu Lys Lys Glu Pro Asp Ala Leu **Thr** Leu Leu
385 390 395 400
Ala Pro Ala Ala Gly Asp **Thr** Ile Ile Ser Leu Asp Phe Gly Ser Asn
405 410 415
Asp **Thr** Glu **Thr** Asp Asp Gln Gln Leu Glu Glu Val Pro Leu Tyr
Asn
420 425 430
Asp Val Met Leu Pro Ser Pro Asn Glu Lys Leu Gln Asn Ile Asn Leu
435 440 445
Ala Met Ser Pro Leu Pro **Thr** Ala Glu **Thr** Pro Lys Pro Leu Arg
Ser
450 455 460
Ser Ala Asp Pro Ala Leu Asn Gln Glu Val Ala Leu Lys Leu Glu Pro
465 470 475 480
Asn Pro Glu Ser Leu Glu Leu Ser Phe **Thr** Met Pro Gln Ile Gln Asp
485 490 495
Gln **Thr** Pro Ser Pro Ser Asp Gly Ser **Thr** Arg Gln Ser Ser Pro
Glu
500 505 510
Pro Asn Ser Pro Ser Glu Tyr Cys Phe Tyr Val Asp. . . Asp Met Val
515 520 525
Asn Glu Phe Lys Leu Glu Leu Val Glu Lys Leu Phe Ala Glu Asp **Thr**
530 535 540
Glu Ala Lys Asn Pro Phe Ser **Thr** Gln Asp **Thr** Asp Leu Asp Leu
Glu
545 550 555 560
Met Leu Ala Pro Tyr Ile Pro Met Asp Asp Asp Phe Gln. . . Leu Ser Pro Leu Glu
Ser Ser Ser Ala Ser Pro Glu Ser
580 585 590
Ala Ser Pro Gln Ser **Thr** Val **Thr** Val Phe Gln Gln **Thr**

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       Gln Ile Gln
        595                 600                 605
Glu Pro Thr Ala Asn Ala Thr Thr Thr
       Thr Ala Thr Thr Asp Glu Leu
    610                 615                 620
Lys Thr Val Thr Lys Asp Arg Met Glu Asp Ile Lys Ile Leu Ile
       Ala
625                 630                 635                 640
Ser Pro Ser Pro Thr His Ile His Lys Glu Thr Thr
       Ser Ala Thr Ser
                645                 650                 655
Ser Pro Tyr Arg Asp Thr Gln Ser Arg Thr Ala Ser Pro Asn Arg
       Ala
            660                 665                 670
Gly Lys Gly Val Ile Glu Gln Thr Glu Lys Ser His Pro Arg Ser Pro
        675                 680                 685
Asn Val Leu Ser Val Ala Leu Ser Gln Arg Thr Thr Val Pro Glu
       Glu
    690                 695                 700
Glu Leu Asn Pro Lys Ile Leu Ala Leu Gln Asn Ala Gln Arg Lys Arg
705                 710                 715                 720
Lys Met Glu His Asp Gly Ser Leu Phe Gln Ala Val Gly Ile Gly Thr
                725                 730                 735
Leu Leu Gln Gln Pro Asp Asp His Ala Ala Thr Thr Ser Leu Ser
       Trp
            740                 745                 750
Lys Arg Val Lys Gly Cys Lys Ser Ser Glu Gln Asn Gly Met Glu Gln
        755                 760                 765
Lys Thr Ile Ile Leu Ile Pro Ser Asp Leu Ala Cys Arg Leu Leu Gly
    770                 775                 780
Gln Ser Met Asp Glu Ser Gly Leu Pro Gln Leu Thr Ser Tyr Asp Cys
785                 790                 795                 800
Glu Val Asn Ala Pro Ile Gln Gly Ser Arg Asn Leu Leu Gln.  .  .
```

L12 ANSWER 5 OF 63 USPATFULL

ACCESSION NUMBER:	2002:63687 USPATFULL		
TITLE:	Prognostic compositions for prostate cancer and methods of use thereof		
INVENTOR(S):	Tricoli, James V., 106 Clover Leaf La., North Wales, PA, United States 19454 Rondinelli, Rachel, 418 Candlewood Way, Harleysville, PA, United States 19438		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6361948	B1	20020326
	WO 9909215		19990225 <--
APPLICATION INFO.:	US 2000-485549		20001109 (9)
	WO 1998-US16768		19980813
			20001109 PCT 371 date
	NUMBER		DATE
PRIORITY INFORMATION:	US 1997-55285P		19970813 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Horlick, Kenneth R.		
LEGAL REPRESENTATIVE:	Dean Dorfman Herrell & Skillman		
NUMBER OF CLAIMS:	19		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	12 Drawing Figure(s); 8 Drawing Page(s)		
LINE COUNT:	1789		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI	US 6361948	B1	20020326
	WO 9909215	19990225	<--

SUMM A third type of target cell for transgene introduction is the embryonal stem cell (ES). ES cells are obtained from pre-**implantation** embryos cultured in vitro (Evans, M. J., et al., (1981) Nature 292, 154-156; Bradley, A., et al. (1984) Nature 309,. . .

DETD . . . cDNA, genomic DNA, RNA, and fragments thereof which may be single- or double-stranded. Thus, this invention provides oligonucleotides (sense or **antisense** strands of DNA or RNA) having sequences capable of hybridizing with at least one sequence of a nucleic acid molecule. . .

DETD . . . one embodiment, the nucleic acid molecules of the invention may be used to decrease expression of CLAR1. In this embodiment, **antisense** molecules are employed which are targeted to expression-controlling sequences of CLAR1-encoding genes. **Antisense** oligonucleotides may be designed to hybridize to the complementary sequence of nucleic acid, pre-mRNA or mature mRNA, interfering with the. . . or variant form thereof), so that its expression is reduced or prevented altogether. In addition to the CLAR1 coding sequence, **antisense** techniques can be used to target the control sequences of the CLAR1 gene, e.g. the 5' flanking sequence of the CLAR1 coding sequence such as the translation start site. **Antisense** oligomers should be sufficient length to hybridize to the target nucleotide sequence and exert the desired effect, e.g. blocking translation. . . smaller oligomers are likely to be more efficiently taken up by cells in vivo such that a greater number of **antisense** oligomers may be delivered to the location of the target mRNA. Preferably, **antisense** oligomers should be at least 15 nucleotides long to achieve adequate specificity. Oligonucleotides for use in **antisense** technology are preferably between 15 to 30 nucleotides in length. The use of **antisense** molecules to decrease expression levels of a pre-determined gene is known in the art. The construction of **antisense** sequences and their use is described in Peyman and Ulman, Chemical Reviews, 90:543-584, (1990), Crooke, Ann. Rev. Pharmacol. Toxical., 32:329-376, (1992), and Zamecnik and Stephenson, P.N.A.S., 75:280-284, (1974). Examples of **antisense** sequences for the two spliced forms of CLAR1 (SEQ ID NO: 2 and SEQ ID NO: 3) include:

DETD . . . multiple organ northern blots (CLONTECH) that contain 2 .mu.g of poly(A+) RNA from adult pancreas, kidney, skeletal muscle, liver, lung, **placenta**, brain, heart, peripheral blood leukocyte, colon, small intestine, ovary, testis, prostate, thymus, spleen and fetal kidney, liver, lung and brain. . .

DETD . . . His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, **Thr**; V, Val; W, Trp and Y, Tyr.

DETD . . . 2

LENGTH: 276

TYPE: PRT

ORGANISM: Homo sapiens

SEQUENCE: 2

```
Met Ser Phe Glu Gly Gly Asp Gly Ala Gly Pro Ala Met Leu Ala Thr
 1               5                  10                  15
Gly Arg Ala Arg Met Ala Ser Gly Arg Pro Glu Glu Leu Trp Glu Ala
            20                  25                  30
Val Val Gly Ala Ala Glu Arg Phe Arg Ala Arg Thr Gly Thr Glu
        Leu
         35                  40                  45
Val Leu Leu Thr Ala Ala Pro Pro Pro Pro Pro Arg Pro Gly Pro Cys
    50                  55                  60
Ala Tyr Ala Ala His Gly. . . Ala Glu Ala Ala Arg Arg
65                  70                  75                  80
Cys Leu His Asp Ile Ala Leu Ala His Arg Ala Ala Thr Ala Ala Arg
                85                  90                  95
Leu Pro Ala Pro Pro Pro Ala Pro Gln Pro Pro Ser Pro Thr Pro Ser
            100                 105                 110
Pro Pro Arg Pro Thr Leu Ala Arg Glu Asp Asn Glu Glu Asp Glu Asp
```

```
        115                 120                 125
Glu Pro Thr Glu Thr Glu Thr Ser Gly Glu Gln Leu
       Gly Ile Ser Asp
    130                 135                 140
Asn Gly Gly Leu Phe Val Met Asp Glu Asp Ala Thr Leu Gln Asp Leu
145                 150                 155                 160
Pro Pro Phe Cys Glu Ser Asp Pro Glu Ser Thr Asp Asp Gly Ser Leu
                165                 170                 175
Ser Glu Glu Thr Pro Ala Gly Pro Pro Thr Cys Ser Val Pro Pro
       Ala
            180                 185                 190
Ser Ala Leu Pro Thr Gln Gln Tyr Ala Lys Ser Leu Pro Val Ser Val
        195                 200                 205
Pro Val Trp Gly Phe Lys Glu Lys Arg Thr Glu Ala Arg Ser Ser Asp
    210                 215                 220
Gly Glu Asn Gly Pro Pro Ser Ser Pro Asp Leu Asp Arg Ile Ala Ala
225                 230                 235                 240
Ser Met Arg Ala Leu Val Leu Arg Glu Ala Glu Asp Thr Gln Val Phe
                245                 250                 255
Gly Asp Leu Pro Arg Pro Arg Leu Asn Thr Ser Asp Phe Gln Lys Leu
            260                 265                 270
Lys Arg Lys Tyr
        275
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 3
LENGTH: 256
TYPE: PRT
ORGANISM: Homo.  .  .  Glu Glu Leu Trp Glu Ala Val Val Gly Ala
 1               5                   10                  15
Ala Glu Arg Phe Arg Ala Arg Thr Gly Thr Glu Leu Val Leu Leu
       Thr
            20                  25                  30
Ala Ala Pro Pro Pro Pro Pro Arg Pro Gly Pro Cys Ala Tyr Ala Ala
        35                  40.  .  .  Ala Glu Ala Ala Arg Arg Cys Leu His Asp
    50                  55                  60
Ile Ala Leu Ala His Arg Ala Ala Thr Ala Ala Arg Leu Pro Ala Pro
65                  70                  75                  80
Pro Pro Ala Pro Gln Pro Pro Ser Pro Thr Pro Ser Pro Pro Arg Pro
                85                  90                  95
  Thr Leu Ala Arg Glu Asp Asn Glu Glu Asp Glu Asp Glu Pro Thr
       Glu
            100                 105                 110
  Thr Glu Thr Ser Gly Glu Gln Leu Gly Ile Ser Asp Asn Gly Gly
       Leu
        115                 120                 125
Phe Val Met Asp Glu Asp Ala Thr Leu Gln Asp Leu Pro Pro Phe Cys
    130                 135                 140
Glu Ser Asp Pro Glu Ser Thr Asp Asp Gly Ser Leu Ser Glu Glu
       Thr
145                 150                 155                 160
Pro Ala Gly Pro Pro Thr Cys Ser Val Pro Pro Ala Ser Ala Leu Pro
                165                 170                 175
  Thr Gln Gln Tyr Ala Lys Ser Leu Pro Val Ser Val Pro Val Trp Gly
            180                 185                 190
Phe Lys Glu Lys Arg Thr Glu Ala Arg Ser Ser Asp Gly Glu Asn Gly
        195                 200                 205
Pro Pro Ser Ser Pro Asp Leu Asp Arg Ile Ala Ala Ser Met Arg Ala
    210                 215                 220
Leu Val Leu Arg Glu Ala Glu Asp Thr Gln Val Phe Gly Asp Leu Pro
225                 230                 235                 240
Arg Pro Arg Leu Asn Thr Ser Asp Phe Gln Lys Leu Lys Arg Lys Tyr
                245                 250                 255
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 4
LENGTH: 20
```

TYPE: DNA
ORGANISM: Homo. . .

L12 ANSWER 6 OF 63 USPATFULL
ACCESSION NUMBER: 2001:102606 USPATFULL
TITLE: Synthetic mammalian .alpha.-n-acetylglucosaminidase and genetic sequences encoding same
INVENTOR(S): Hopwood, John Joseph, Stonyfell, Australia
Scott, Hamish Steele, Geneva, Switzerland
Weber, Birgit, Hackney, Australia
Blanch, Lianne, Grange, Australia
Anson, Donald Stewart, Thebarton, Australia
PATENT ASSIGNEE(S): Women's and Children's Hospital, Australia (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6255096	B1	20010703	
	WO 9719177		19970529	<--
APPLICATION INFO.:	US 1999-77354		19990422	(9)
	WO 1996-AU747		19961122	
			19990422	PCT 371 date
			19990422	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	AU 1995-6748	19951123

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Rao, Manjunath
LEGAL REPRESENTATIVE: Pokalsky, Ann R.
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1469
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6255096 B1 20010703
WO 9719177 19970529 <--
DRWD FIG. 1 is a photographic representation of .alpha.-N-acetylglucosaminidase purified from human **placenta** following SDS/PAGE. Lane 1: M.sub.r standards (kDa); Lanes 2 and 3: purified .alpha.-N-acetylglucosaminidase from human **placenta**. Lane 4 and 5, bovine serum albumin.
DRWD . . . I

Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	**Thr**	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V
Any residue	Xaa	X

DRWD . . . His

Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn; Gln
Ile	Leu; Val
Leu	Ile; Val

Lys	Arg; Gln; Glu
Met	Leu; Ile
Phe	Met; Leu; Tyr
Ser	**Thr**
Thr	Ser
Trp	Tyr
Tyr	Trp; Phe
Val	Ile; Leu

DETD . . . or guinea pig). Most preferably, the mammal is a human. Conveniently, the .alpha.-N-acetylglucosaminidase is isolatable from the liver, kidney or **placenta**. However, the present invention extends to all mammalian .alpha.-N-acetylglucosaminidase enzymes and from any anatomical or cellular source and/or any biological. . .

DETD . . . SEQ ID NO:3 or a homologue, derivative or analogue thereof and the second primer molecule is preferably derived from the **antisense** strand of said gene.

DETD . . . for enzyme therapy may be by oral, intravenous, suppository, intraperitoneal, intramuscular, intranasal, intradermal or subcutaneous administration or by infusion or **implantation**. The .alpha.-N-acetylglucosaminidase is preferably as hereinbefore described including active mutants or derivatives thereof and glycosylation variants thereof. Administration may also. . .

DETD .alpha.-N-acetylglucosaminidase was purified according to the method described in Weber et al. (1996). Enzyme was purified to homogeneity from human **placenta**. Evidence of purity is shown following SDS/PAGE which is represented in FIG. 1. All samples were reduced with dithiothreitol prior. . .

DETD . . . show two polypeptides of about 82 kDa and 77 kDa molecular weight, which correspond to .alpha.-N-acetylglucosaminidase polypeptides purified from human **placenta** according to Example 1.

CLM What is claimed is:

5. The isolated nucleic acid molecule of claim 1 isolated from liver, kidney or **placenta**.

L12 ANSWER 7 OF 63 USPATFULL

ACCESSION NUMBER:	2001:71683 USPATFULL
TITLE:	Persephin and related growth factors
INVENTOR(S):	Johnson, Jr., Eugene M., St. Louis, MO, United States Milbrandt, Jeffrey D., St. Louis, MO, United States Kotzbauer, Paul T., Swarthmore, PA, United States Lampe, Patricia A., St. Louis, MO, United States
PATENT ASSIGNEE(S):	Washington University, St. Louis, MO, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6232449	B1	20010515	
	WO 9733911		19970918	<--
APPLICATION INFO.:	US 1998-981739		19980831	(8)
	WO 1997-US3461		19970314	
			19980831	PCT 371 date
			19980831	PCT 102(e) date

RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1996-615944, filed on 14 Mar 1996, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Chan, Christina Y.
ASSISTANT EXAMINER:	Hayes, Robert C.
LEGAL REPRESENTATIVE:	Howell & Haferkamp, L.C.
NUMBER OF CLAIMS:	6
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	28 Drawing Figure(s); 27 Drawing Page(s)
LINE COUNT:	3790

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 6232449 B1 20010515
WO 9733911 19970918 <--

DETD . . . or Cys (SEQ ID NO:4); (2) with uncertainty as to positions 1, 2, 4, 10, 17 and 22, Xaa.sub.1 -Xaa.sub.2 -Val-Glu-Ala-Lys-Pro-Cys-Cys-Gly-Pro-**Thr**-Ala-Tyr-Glu-Asp-Xaa.sub.3 -Val-Ser-Phe-Leu-Ser-Val where Xaa.sub.1 and Xaa.sub.2 were unknown, Xaa.sub.3 was Gln or Glu (SEQ ID NO:5) and (3) Tyr-His-**Thr**-Leu-Gln-Glu-Leu-Ser-Ala-Arg (SEQ ID NO:6). Based upon these partial amino acid sequences, DNA probes and primers can be made and used to. . .

DETD . . . at specific receptors. For example, the receptors for TGF-.beta. and activins have been identified and make up a family of Ser/**Thr** kinase transmembrane proteins (Kingsley, Genes and Dev 8:133-146, 1994; Bexk et al Nature 373:339-341, 1995 which are incorporated by reference).. . .

DETD Conserved-region amino acid sequences have been identified herein to include Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Tyr where Xaa.sub.1 is Ser, **Thr** or Ala and Xaa.sub.2 is Glu or Asp (SEQ ID NO:108); Glu-Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Arg-Tyr-Cys-Xaa.sub.4 -Gly-Xaa.sub.5 -Cys in which Xaa.sub.1 is **Thr**, Glu or lys, Xaa.sub.2 is Val, Leu or Ile, Xaa.sub.3 is Leu or Ile, Xaa.sub.4 is Ala or Ser, and. . . NO:113); and Cys-Cys-Xaa.sub.1 -Pro-Xaa.sub.2 -Xaa.sub.3 -Xaa.sub.4 -Xaa.sub.5 -Asp-Xaa.sub.6 -Xaa.sub.7 -Xaa.sub.8 -Phe-Leu-Asp-Xaa.sub.9 in which Xaa.sub.1 is Arg or Gln, Xaa.sub.2 is **Thr** or Val or Ile, Xaa.sub.3 is Ala or Ser, Xaa.sub.4 is Tyr or Phe, Xaa.sub.5 is Glu, Asp or Ala, Xaa.sub.6 is Glu, Asp or no amino acid, Xaa.sub.7 is val or leu, Xaa.sub.8 is Ser or **Thr**, and Xaa.sub.9 is Asp or Val (SEQ ID NO:114). Nucleotide sequences containing a coding sequence for the above conserved sequences. . .

DETD . . . anticipated to have at least a 62.5% identity with the consensus region octapeptide, Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Tyr where Xaa.sub.1 is Ser, **Thr** or Ala and Xaa.sub.2 is Glu or Asp (SEQ ID NO:108) or at least a 62.5 percent sequence identity with. . .

DETD . . . for mature persephin or neurturin protein. The term complementary to a nucleotide sequence in the context of persephin or neurturin **antisense** oligonucleotides and methods therefor means sufficiently complementary to such a sequence as to allow hybridization to that sequence in a cell, i.e., under physiological conditions. The persephin or neurturin **antisense** oligonucleotides preferably comprise a sequence containing from about 8 to about 100 nucleotides and more preferably the persephin or neurturin **antisense** oligonucleotides comprise from about 15 to about 30 nucleotides. The persephin or neurturin **antisense** oligonucleotides can also contain a variety of modifications that confer resistance to nucleolytic degradation such as, for example, modified internucleoside. . .

DETD . . . neurturin by the body. In one approach cells that secrete persephin or neurturin may be encapsulated into semipermeable membranes for **implantation** into a patient. The cells can be cells that normally express persephin or neurturin or a precursor thereof or the. . .

DETD . . . sequences from reverse transcribed MRNA. A forward primer (M1676; 5'-CCNACNGCNTAYGARGA, SEQ ID NO:50) corresponding to peptide sequence P2 Xaa.sub.1 -Xaa.sub.2 -Val-Glu-Ala-Lys-Pro-Cys-Cys-Gly-Pro-**Thr**-Ala-Tyr-Glu-Asp-Xaa.sub.3 -Val-Ser-Phe-Leu-Ser-Val where Xaa.sub.1 and Xaa.sub.2 were unknown, Xaa.sub.3 was Gln or Glu (SEQ ID NO:5) in combination with a reverse primer (M1677; 5'-ARYTCYTGNARNGTRTGRTA (SEQ ID NO:52) corresponding to peptide sequence P3 (Tyr-His-**Thr**-Leu-Gln-Glu-Leu-Ser-Ala-Arg) (SEQ ID NO:6) were used to amplify a 69 nucleotide product from cDNA templates derived from E21 rat and adult. . .

DETD . . . +

Spleen	-	+
Cerebellum	-	-
Uterus	++	-

Bone marrow	++	-	
Testis	++	++	
Ovary	+		+
Placenta		+	-
Skeletal muscle	+		-
Spinal cord	+		-
Adrenal gland	++	++	
Gut	+		++

DETD . . . probes or primers. Conserved-region amino acid sequences have been identified herein to include Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Tyr where Xaa.sub.1 is Ser, **Thr** or Ala and Xaa.sub.2 is Glu or Asp (SEQ ID NO:108); Glu-Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Arg-Tyr-Cys-Xaa.sub.4 -Gly-Xaa.sub.5 -Cys in which Xaa.sub.1 is **Thr**, Glu or lys, Xaa.sub.2 is Val, Leu or Ile, Xaa.sub.3 is Leu or Ile, Xaa.sub.4 is Ala or Ser, and. . . NO:113); and Cys-Cys-Xaa.sub.1 -Pro-Xaa.sub.2 -Xaa.sub.3 -Xaa.sub.4 -Xaa.sub.5 -Asp-Xaa.sub.6 -Xaa.sub.7 -Xaa.sub.8 -Phe-Leu-Asp-Xaa.sub.9 in which Xaa.sub.1 is Arg or Gln, Xaa.sub.2 is **Thr** or Val or Ile, Xaa.sub.3 is Ala or Ser, Xaa.sub.4 is Tyr or Phe, Xaa.sub.5 is Glu, Asp or Ala, Xaa.sub.6 is Glu, Asp or no amino acid, Xaa.sub.7 is val or leu, Xaa.sub.8 is Ser or **Thr**, and Xaa.sub.9 is Asp or Val (SEQ ID NO:114). Nucleotide sequences containing a coding sequence for the above conserved sequences. . .

DETD . . . (M3119): 5'-GTNDGNGANYTGGGNYTGGGNTA (SEQ ID NO:115) 23 nt which codes for the amino acid sequence, Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Tyr where Xaa.sub.1 is **Thr**, Ser or Ala and Xaa.sub.2 is Glu or Asp (SEQ ID NO:125);

DETD . . . acid sequence, Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Leu-Xaa.sub.4 -Xaa.sub.5 where Xaa.sub.1 is Asp or Glu, Xaa.sub.2 is Val or Leu, Xaa.sub.3 is **Thr** or Ser, Xaa.sub.4 is Asp or Glu, and Xaa.sub.5 is Asp or Val (SEQ ID NO:126);

DETD . . . (M3122): 5'-GTNDGNGANYTGGGNYTNGG (SEQ ID NO:119) 20 nt which codes for the amino acid sequence, Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly where Xaa.sub.1 is **Thr**, Ser or Ala and Xaa.sub.2 is Asp or Glu (SEQ ID NO:128); and

DETD . . . (M3176): 5'-GTNDGNGANYTGGGNYTGGGNTT (SEQ ID NO:120) 23 nt which codes for the amino acid sequence, Val-Xaa.sub.2 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Phe where Xaa.sub.1 is **Thr**, Ser or Ala and Xaa.sub.2 is Glu or Asp (SEQ ID NO:12 9).

DETD . . . acid sequence, Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Leu-Xaa.sub.4 -Xaa.sub.5 where Xaa.sub.1 is Asp or Glu, Xaa.sub.2 is Val or Leu, Xaa.sub.3 is **Thr** or Ser, Xaa.sub.4 is Asp or Glu, and Xaa.sub.1 is Asp or Val (SEQ ID NO:126);

DETD . . . acid sequence, Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Leu-Xaa.sub.4 -Xaa.sub.5 where Xaa.sub.1 is Asp or Glu, Xaa.sub.2 is Val or Leu, Xaa.sub.3 is **Thr** or Ser, Xaa.sub.4 is Asp or Glu, and Xaa.sub.5 is Asp or Val (SEQ ID NO:126);

DETD Primer 1, GTNWSNGANYTNGGNYTNGGNTA (SEQ ID NO:42) which encodes the amino acid sequence, Val-Xaa.sub.1 -Xaa.sub.2 -Leu-Gly-Leu-Gly-Tyr where Xaa.sub.1 is Ser or **Thr** and Xaa.sub.2 is Glu or Asp (SEQ ID NO:33);

DETD . . . (SEQ ID NO:45) whose reverse complementary sequence encodes amino acid sequence Cys-Cys-Arg-Pro-Xaa.sub.1 -Ala-Xaa.sub.2 -Xaa.sub.3 -Asp-Xaa.sub.4 where Xaa.sub.1 is Ile or **Thr** or Val, Xaa.sub.2 Try or Phe, Xaa.sub.3 is Glu or Asp and Xaa.sub.4 is Glu or Asp (SEQ ID NO:38);

DETD Primer 6 GARRMNBTNHTNTTYMGNTAYTG (SEQ ID NO:47) which encodes amino acid sequence Glu-Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Arg-Tyr-Cys where Xaa.sub.1 is Glu or **Thr**, Xaa.sub.2 is Leu or Val and Xaa.sub.3

is Ile or Leu (SEO ID NO:40);

DETD . . . GARRMNBTNHTNTTYMGNTAYTGYDSNGGNDSNTGHGA (SEQ ID NO:48) which encodes amino acid sequence Glu-Xaa.sub.1 -Xaa.sub.2 -Xaa.sub.3 -Phe-Arg-Tyr-Cys-Xaa.sub.4 -Gly-Xaa.sub.5 -Cys-Xaa.sub.6 where Xaa.sub.1 is Glu or **Thr**, Xaa.sub.2 is Leu or Val, Xaa.sub.3 is Ile or Leu, Xaa.sub.4 is Ser or Ala, Xaa.sub.5 is Ser or Ala. . .

DETD . . . is provided in greater detail as follows. Primers corresponding to the amino acid sequence Val-Xaa1-Xaa2-Leu-Gly-Leu-Gly-Tyr where Xaa1 is Ser or **Thr** and Xaa2 is Glu or Asp (SEQ ID NO:33) [M1996; 5'-GTNWSNGANYTNGGNYTNGGNTA (SEQ ID NO:42)] and Phe-Arg-Tyr-Cys-Xaa1-Gly-Xaa2-Cys-Xaa3-Xaa4-Ala where Xaa1 is Ala. . .

L12 ANSWER 8 OF 63 USPATFULL

ACCESSION NUMBER: 2001:60112 USPATFULL

TITLE: Transgenic non-human mammal expressing the DNA sequence encoding kappa casein mammary gland and milk

INVENTOR(S): Hansson, Lennart, Ume.ang., Sweden
Stromqvist, Mats, Ume.ang., Sweden
Bergstrom, Sven, Ume.ang., Sweden
Hernell, Olle, Ume.ang., Sweden
Tornell, Jan, Vastra, Sweden

PATENT ASSIGNEE(S): Symbicom Aktiebolag, Umea, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6222094	B1	20010424	
	WO 9315196		19930805	<--
APPLICATION INFO.:	US 1994-256799		19941206	(8)
	WO 1993-DK24		19930125	
			19941206	PCT 371 date
			19941206	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1992-88	19920123

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Crouch, Deborah

LEGAL REPRESENTATIVE: Cooper, Iver P.

NUMBER OF CLAIMS: 26

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 18 Drawing Figure(s); 18 Drawing Page(s)

LINE COUNT: 3140

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 6222094 B1 20010424
WO 9315196 19930805 <--

SUMM . . . functions or by introduction of vectors encoding RNA sequences which are complementary to endogenous glycosyltransferase mRNA species, thereby function as **antisense** RNA.

SUMM Glycosylation is normally found in connection with amino acid residues Asn, Ser, **Thr** or hydroxylysine.

SUMM . . . this preferred embodiment, the fertilized oocytes are first microinjected by standard techniques. They are thereafter cultured in vitro until a "pre-**implantation** embryo" is obtained. Such pre-**implantation** embryos preferably contain approximately 16 to 150 cells. The 16 to 32 cell stage of an embryo is commonly referred to as a morula. Those pre-**implantation** embryos containing more than 32 cells are commonly referred to as blastocysts. They are generally characterized as demonstrating the development of a blastocoel cavity typically at the 64 cell stage. Methods for culturing fertilized oocytes to the pre-**implantation** stage include those described by Gordon et al. (1984), Methods in Enzymology, 101, 414; Hogan et al. (1986) in Manipulating. . . al (1984) J. Reprod. Fert. 72, 779-785; and Heyman, Y. et al. (1987) Theriogenology 27, 5968 (for bovine

embryos). Such pre-**implantation** embryos are thereafter transferred to an appropriate female by standard methods to permit the birth of a transgenic or chimeric. . .

SUMM Since the frequency of transgene incorporation is often low, the detection of transgene integration in the pre-**implantation** embryo is highly desirable. In one aspect of the invention, methods are provided for identifying embryos wherein transgenesis has occurred and which permit **implantation** of transgenic embryos to form transgenic animals. In this method, one or more cells are removed from the pre-**implantation** embryo. When equal division is used, the embryo is preferably not cultivated past the morula stage (32 cells). Division of the pre-**implantation** embryo (reviewed by Williams et al. (1984) Theriogenology 22, 521-531) results in two "hemi-embryos" (hemi-morula or hemi-blastocyst) one of which is capable of subsequent development after **implantation** into the appropriate female to develop in utero to term. Although equal division of the pre-**implantation** embryo is preferred, it is to be understood that such an embryo may be unequally divided either intentionally or unintentionally. . .

SUMM One of each of the hemi-embryos formed by division of pre-**implantation** embryos is analyzed to determine if the transgene has been integrated into the genome of the organism. Each of the other hemi-embryos is maintained for subsequent **implantation** into a recipient female of the species.

SUMM The identification of the pre-**implantation** embryos containing the integrated transgene is achieved by analyzing the DNA from one of each of the hemi-embryos. Such DNA. . . of the amplified DNA sequences, if any, and provides an indication of whether the transgene has been integrated into the pre-**implantation** embryo from which the hemi-embryo was obtained (now called a "transgenic hemi-embryo"). If it has, the remaining untreated transgenic hemi-embryo. . .

SUMM The above described methods for the detection of transgenesis in pre-**implantation** embryos provide economical and time saving methods for generating transgenic non-human animals since they significantly decrease the number of pregnancies. . .

SUMM In an alternate embodiment, the above described method for detecting transgenesis in pre-**implantation** embryos is combined with embryonic cloning steps to generate a clonal population of transgenic embryos which may thereafter be implanted. . .

SUMM . . . transgenic hemi-embryo is cultured in the same or in a similar medium as used to culture individual oocytes to the pre-**implantation** stage. The "transgenic embryo" so formed (preferably a transgenic morula) is then divided into "transgenic hemi-embryos" which can then be. . . a clonal population of two transgenic non-human animals. Alternatively, the two transgenic hemi-embryos obtained may be again cultivated to the pre-**implantation** stage, divided, and recultivated to the transgenic embryo stage. This procedure is repeated until the desired number of clonal transgenic. . .

SUMM . . . also be performed transvaginally and under echoscopic guidance. In this method, a needle is used to puncture the recipient animal's **placenta**, particularly the placentonal structures, which are fixed against the vaginal wall. Such sampling may be performed around day 60 of. . .

DETD . . . DNA were screened and analyzed. Human genomic libraries were obtained from Clontech (Palo Alto, USA). The libraries were constructed from **placenta** DNA (catalog #HL1067J) or female leukocyte DNA (catalog #HL1111J), cloned into .lambda.EMBL-3 vector. The average size of inserts are 15. . .

L12 ANSWER 9 OF 63 USPATFULL
ACCESSION NUMBER: 2000:18625 USPATFULL
TITLE: Transgenic non-human mammals producing EC-SOD protein in their milk

INVENTOR(S):	Hansson, Lennart, Bjorkvagen 50, S-902 40 Ume.ang., Sweden			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6025540		20000215	
	WO 9500637		19950105	<--
APPLICATION INFO.:	US 1995-556965		19951207	(8)
	WO 1994-IB181		19940624	
			19951207	PCT 371 date
			19951207	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	DK 1993-753	19930624

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Priebe, Scott D.
ASSISTANT EXAMINER: Wilson, Michael C.
LEGAL REPRESENTATIVE: Cooper, Iver P.
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 2719
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 6025540 20000215
WO 9500637 19950105 <--

SUMM . . . functions or by introduction of vectors encoding RNA sequences which are complementary to endogenous glycosyltransferase mRNA species, thereby function as **antisense** RNA.

SUMM . . . this preferred embodiment, the fertilized oocytes are first microinjected by standard techniques. They are thereafter cultured in vitro until a "pre-**implantation** embryo" is obtained. Such pre-**implantation** embryos preferably contain approximately 16 to 150 cells. The 16 to 32 cell stage of an embryo is commonly referred to as a morula. Those pre-**implantation** embryos containing more than 32 cells are commonly referred to as blastocysts. They are generally characterized as demonstrating the development of a blastocoel cavity typically at the 64 cell stage. Methods for culturing fertilized oocytes to the pre-**implantation** stage include those described by Gordon et al. [58]; Hogan et al. [41] (for the mouse embryo); and Hammer et. . . ovine embryos); and Eyestone et al. [62]; Camous et al. [63]; and Heyman et al. [64] (for bovine embryos). Such pre-**implantation** embryos are thereafter transferred to an appropriate female by standard methods to permit the birth of a transgenic or chimeric. . .

SUMM Since the frequency of transgene incorporation is often low, the detection of transgene integration in the pre-**implantation** embryo is highly desirable. In one aspect of the invention, methods are provided for identifying embryos wherein transgenesis has occurred and which permit **implantation** of transgenic embryos to form transgenic animals. In this method, one or more cells are removed from the pre-**implantation** embryo. When equal division is used, the embryo is preferably not cultivated past the morula stage (32 cells). Division of the pre-**implantation** embryo (reviewed by Williams et al. [65]) results in two "hemi-embryos" (hemi-morula or hemi-blastocyst) one of which is capable of subsequent development after **implantation** into the appropriate female to develop in utero to term. Although equal division of the pre-**implantation** embryo is preferred, it is to be understood that such an embryo may be unequally divided either intentionally or unintentionally. . .

SUMM One of each of the hemi-embryos formed by division of pre-**implantation** embryos is analyzed to determine if the transgene has been integrated into the genome of the organism. Each of the other hemi-embryos is maintained for subsequent **implantation** into a

recipient female of the species.

SUMM The early identification of the pre-**implantation** embryos containing the integrated transgene is achieved by analyzing the DNA from one of each of the hemi-embryos. Such DNA. . . of the amplified DNA sequences, if any, and provides an indication of whether the transgene has been integrated into the pre-**implantation** embryo from which the hemi-embryo was obtained (now called a "transgenic hemi-embryo"). If it has, the remaining untreated transgenic hemi-embryo. . .

SUMM The above described methods for the detection of transgenesis in pre-**implantation** embryos provide economical and time saving methods for generating transgenic non-human animals since they significantly decrease the number of pregnancies. . .

SUMM In an alternate embodiment, the above described method for detecting transgenesis in pre-**implantation** embryos is combined with embryonic cloning steps to generate a clonal population of transgenic embryos which may thereafter be implanted. . .

SUMM . . . transgenic hemi-embryo is cultured in the same or in a similar medium as used to culture individual oocytes to the pre-**implantation** stage. The "transgenic embryo" so formed (preferably a transgenic morula) is then divided into "transgenic hemi-embryos" which can then be. . . a clonal population of two transgenic non-human animals. Alternatively, the two transgenic hemi-embryos obtained may be again cultivated to the pre-**implantation** stage, divided, and recultivated to the transgenic embryo stage. This procedure is repeated until the desired number of clonal transgenic. . .

SUMM . . . also be performed transvaginally and under echoscopic guidance. In this method, a needle is used to puncture the recipient animal's **placenta**, particularly the placentonal structures, which are fixed against the vaginal wall. Such sampling may be performed around day 60 of. . .

DETD . . . - TGG ACG GGC GAG GAC TCG GCG GAG CCC AAC TC - #T GAC TCG GCG
GAG
TGG 48
Trp **Thr** Gly Glu Asp Ser Ala Glu Pro Asn Se - #r Asp Ser Ala Glu Trp
1 5 - #. . . GTC ACG GAG AT - #C TGG CAG GAG GTC ATG
96
Ile Arg Asp Met Tyr Ala Lys Val **Thr** Glu Il - #e Trp Gln Glu Val Met
20 - # 25 - # 30
- - CAG CGG. . . GGC ACG CTC CAC GC - #C GCC TGC CAG GTG CAG
144
Gln Arg Arg Asp Asp Asp Gly **Thr** Leu His Al - #a Ala Cys Gln Val Gln
35 - # 40 - # 45
- - CCG. . . GCC ACG CTG GAC GCC GCG CAG CCC CG - #G GTG ACC GGC GTC GTC
192
Pro Ser Ala **Thr** Leu Asp Ala Ala Gln Pro Ar - #g Val **Thr**
Gly Val Val
50 - # 55 - # 60
- - CTC TTC CGG CAG CTT GCG CCC CGC. . . CCG ACC GAG CCG AAC AGC TC - #C
AGC CGC GCC ATC CAC
288
Leu Glu Gly Phe Pro **Thr** Glu Pro Asn Ser Se - #r Ser Arg Ala Ile His
85 - # 90 - # 95
-. . . TCC ACC GGG CCC
336
Val His Gln Phe Gly Asp Leu Ser Gln Gly Cy - #s Glu Ser **Thr** Gly Pro
100 - # 105 - # 110
- - CAC TAC AAC CCG CTG GCC GTG CCG CAC. . . linear
- - (ii) MOLECULE TYPE: protein
- - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #2:
- - Trp **Thr** Gly Glu Asp Ser Ala Glu Pro Asn Se - #r Asp Ser Ala Glu
Trp
1 5 - # 10 - # 15
- - Ile Arg Asp Met Tyr Ala Lys Val **Thr** Glu Il - #e Trp Gln Glu Val

Met
20 - # 25 - # 30
- - Gln Arg Arg Asp Asp Asp Gly **Thr** Leu His Al - #a Ala Cys Gln Val
Gln
35 - # 40 - # 45
- - Pro Ser Ala **Thr** Leu Asp Ala Ala Gln Pro Ar - #g Val **Thr**
Gly Val Val
50 - # 55 - # 60
- - Leu Phe Arg Gln Leu Ala Pro Arg. . . Phe Phe Ala
65 - # 70 - # 75 - # 80
- - Leu Glu Gly Phe Pro **Thr** Glu Pro Asn Ser Se - #r Ser Arg Ala Ile
His
85 - # 90 - # 95
- - Val His Gln Phe Gly Asp Leu Ser Gln Gly Cy - #s Glu Ser **Thr** Gly
Pro
100 - # 105 - # 110
- - His Tyr Asn Pro Leu Ala Val Pro His. . .

L12 ANSWER 10 OF 63 USPATFULL
ACCESSION NUMBER: 1999:170432 USPATFULL
TITLE: Polynucleotide encoding a novel purinergic P.sub.2U receptor
INVENTOR(S): Coleman, Roger, Mountain View, CA, United States
Au-Young, Janice, Berkeley, CA, United States
Stuart, Susan G., Montara, CA, United States
Guegler, Karl J., Menlo Park, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6008039		19991228	<--
APPLICATION INFO.:	US 1995-459046		19950602 (8)	

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hutzell, Paula K.
ASSISTANT EXAMINER: Hayes, Robert C.
LEGAL REPRESENTATIVE: Luther, Barbara J., Billings, Lucy J.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1538
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6008039 19991228 <--
AB . . . invention provides nucleotide and amino acid sequences that identify and encode a novel purinergic P.sub.U2 receptor (PNR) expressed in human **placenta**. The present invention also provides for **antisense** molecules to the nucleotide sequences which encode PNR, expression vectors for the production of purified PNR, antibodies capable of binding. . .
SUMM . . . a short N-terminus with two conserved N-glycosylation sites, a moderately short third internal loop, and a long C-terminus containing a Ser/**Thr**-rich region. All adrenergic receptors elevate cAMP or intracellular calcium.
SUMM Purinergic receptors of the **placenta** are likely found on immune or vascular cells and appear to play an important role in signal transduction and other specialized functions of the **placenta** as briefly described below.
SUMM **Placenta**
SUMM The **placenta** is a thickened discoid temporary organ that acts as the site of interchange of substances between the maternal and fetal. . .
SUMM The **placenta** consists of a fetal part derived from the chorion, one of the extraembryonic surrounding membranes of the conceptus and of a maternal part (decidua basalis) derived from the

region of endometrium that underlies the **implantation** site.
The **placenta** is thus the only organ composed of cells derived
from two individuals. The boundary between maternal and fetal tissues is
marked by extracellular products of necrosis referred to as fibrinoid.
The anatomy of the human **placenta** is discussed in detail in
Benirschke and Kaufmann, (1992) Pathology of the Human **Placenta**
, Springer-Verlag, New York City, pp 542-635.

SUMM . . . that gives rise to the embryo and an outer, single layer of
trophoblast cells that encloses the blastocyst cavity. Following
implantation, trophoblasts become highly invasive, erode and
attach to the secretory endometrium. This invasive process involves
matrix-degrading metalloproteinases (MMPs) and tissue. . .

SUMM The chorion or fetal part of the **placenta** has a chorionic
plate at the point where the chorionic villi arise. The finger-like
villi extend into the endometrial lacuna. . .

SUMM . . . for IgG movement is similar to that of IgA across epithelia.
The transport of various materials, particularly nutrients, by the
placenta is reviewed in Smith et al (1992 Ann Rev Nutrition
12:183-206) and Schneider (1991 Reprod Fertil Dev 3:345-353). The
placenta is more than a simple conduit for nutrients; it engages
in considerable metabolic activity contributing to the quality and
quantity. . .

SUMM The function of the endometrium is to support the **implantation**
and development of the embryo. During each menstrual cycle, the most
superficial layer or functionalis, undergoes dramatic changes in
preparation. . .

SUMM **Implantation** induces a decidual response that is characterized
by pronounced changes in the endometrial stroma. Fibroblast-like cells
transform into large, active. . .

SUMM . . . for both estrogen and progesterone. The effects of estrogen and
progesterone on the endometrium, both during the cycle and following
implantation, are complemented and implemented by a variety of
growth factors. Insulin-like growth factors (IGFs) have a major role in
the. . .

SUMM . . . to and receives venous blood from the lacunae situated between
the villi. Although the maternal blood vessels are open during
implantation, the fetal vessels remain intact. Fetal and
maternal blood do not mix, except on rare occasions at the end of. . .

SUMM At the end of a full-term pregnancy, the **placenta** has the
shape of a thick disk. The umbilical cord usually arises from the center
of the **placenta** and connects the circulation of the fetus with
the fetal placental circulation. Fetal venous blood reaches the
placenta through the two umbilical arteries which branch and
ultimately give rise to the vessels of the chorionic villi. In these. .
.

SUMM The **placenta** is permeable to several substances and normally
transfers oxygen, water, electrolytes, carbohydrates, lipids, proteins,
vitamins, hormones, antibodies, and some drugs. . .

SUMM Soon after **implantation**, fetal villi begin to control maternal
physiology creating an optimal environment for fetal development.
Immediately after **implantation**, the syncytiotrophoblast
synthesizes human chorionic gonadotropin (HCG), a glycoprotein hormone
that mimics the effects of luteinizing hormone (LH) through the. . .

SUMM . . . al (1992) Growth Factors 6:219-231). PDGF may play a role in
cytotrophoblast proliferation. The action of various cytokines on the
placenta is reviewed in Mitchell et al (1993 **Placenta**
14:249-275) and Rutanen (1993 Ann Med 25:343-347).

SUMM Pathology of the **Placenta**

SUMM . . . severe toxemia or eclampsia includes convulsions and coma which
may jeopardize both mother and fetus. The pathological changes of the
placenta found in PIH are decidual arteriolopathy, infarcts,
abruptio **placenta**, and Tenney-Parker changes.

SUMM . . . unknown although it is certain that the disease relates to the
presence of placental tissue, since the delivery of the **placenta**
(or hydatidiform mole) ends the disease process. An obliterative

thickening of arterial walls and a reduced number of small arteries. . .

SUMM Many types of infections by viruses, bacteria, mycoplasmas, or parasites cause pathological changes in the **placenta**. Infections may ascend from the endocervical canal, or they may reach the **placenta** through the maternal blood. Rarely are they acquired by amniocentesis, chorionic villus sampling, amnioscopy, percutaneous umbilical blood sampling, or intrauterine fetal transfusions. Some infections cause gross and microscopic changes of the **placenta** , while others leave few characteristic or specifically recognizable traces.

SUMM Other disorders of the **placenta** include, but are not limited to, abruptio placentae; **placenta** previa; placental or maternal floor infarction; **placenta** accreta, increta, and percreta; extrachorial placentas; chorangioma; chorangiosis; chronic villitis; placental villous edema; widespread fibrosis of the terminal villi; intervillous thrombi; hemorrhagic endovasculitis; erythroblastosis fetalis; and nonimmune fetal hydrops. The pathology of the human **placenta** and decidua is discussed in Benirschke and Kaufmann, (1992) Pathology of the Human **Placenta**, Springer-Verlag, New York City pp. 542-635, and in Naeye (1992), Disorders of the **Placenta**, Fetus, and Neonate: Diagnosis and Clinical Significance, Mosby Year Book, St. Louis Mo.

SUMM . . . P.sub.2U receptor (PNR). Incyte Clone No 179696 was used to identify and clone the full length cDNA (pnr) from the **placenta** cDNA library. The novel purinergic receptor which is the subject of this patent application was identified among the cDNAs derived. . .

SUMM . . . activated or inflamed cells and/or tissues with pnr nucleic acids, fragments or oligomers thereof. Aspects of the invention include the **antisense** DNA of pnr; cloning or expression vectors containing pnr; host cells or organisms transformed with expression vectors containing pnr; a. . .

DETD . . . a unique nucleotide sequence identifying a novel homolog of the human purinergic receptor which was first identified in a human **placenta** cDNA library. The sequence for pnr is shown in SEQ ID NO:1 and is homologous to the GenBank sequence, RNU09402. . . PNR are useful in investigations of and interventions in the normal and abnormal physiologic and pathologic processes which comprise the **placenta** 's role in immunity. Therefore, an assay for upregulated expression of PNR can accelerate diagnosis and proper treatment of conditions. . .

DETD The cDNA inserts from random isolates of the **placenta** library were sequenced in part. Methods for DNA sequencing are well known in the art. Conventional enzymatic methods employed DNA. . .

DETD Analysis of INHERIT.TM. results from randomly picked and sequenced portions of clones from **placenta** library identified Incyte 179696 as a homolog of the purinergic receptor RNU09402. The cDNA insert comprising Incyte 179696 was fully. . .

DETD . . . XL-PCR (Perkin Elmer) procedure. Primers were designed based on known sequence; one primer was synthesized to initiate extension in the **antisense** direction (XLR) and the other to extend sequence in the sense direction (XLS or XLF). The primers allowed the sequence. .

DETD The **placenta** cDNA library was used as a template, and XLR and XLS primers were used to amplify sequences containing the gene. . .

DETD VI **Antisense** Analysis

DETD Knowledge of the correct, complete cDNA sequence of PNR enables its use as a tool for **antisense** technology in the investigation of gene function. Oligonucleotides, cDNA or genomic fragments comprising the **antisense** strand of pnr can be used either in vitro or in vivo to inhibit expression of the mRNA. Such technology is now well known in the art, and **antisense** molecules can be designed at various locations along the nucleotide sequences. By treatment of cells or whole test animals with such **antisense** sequences, the gene of interest can be effectively turned off. Frequently, the function of the gene can be ascertained by. . .

DETD . . . sequences constructed to interrupt transcription of a particular open reading frame, modifications of gene expression can be obtained by designing **antisense** sequences to intron regions, promoter/enhancer elements, or even to trans-acting regulatory genes. Similarly, inhibition can be achieved using Hogeboom base-pairing. . .

DETD . . . amount or distribution of PNR or downstream products of an active signalling cascade. Since PNR was found in a human **placenta** library, it appears to be upregulated in cell types mainly involved in immune protection or defense.

DETD . . . acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

- - (ii) MOLECULE TYPE: cDNA

- - (vii) IMMEDIATE SOURCE:

(A) LIBRARY: **Placenta**

(B) CLONE: 179696

- - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

- - ATGGAATGGG ACAATGGCAC AGACCAGGCT CTGGGCTTGC CACCCACCAC CT - #GTGTCTAC. . . (ii) MOLECULE TYPE: protein

- - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

- - Met Glu Trp Asp Asn Gly **Thr** Asp Gln Ala Le - #u Gly Leu Pro Pro **Thr**

1 5 - # 10 - # 15

- - **Thr** Cys Val Tyr Arg Glu Asn Phe Lys Gln Le - #u Leu Leu Pro Pro Val

20 - #. . . Ala Leu Pro Le - #u Asn Ile Cys Val Ile

35 - # 40 - # 45

- - **Thr** Gln Ile Cys **Thr** Ser Arg Arg Ala Leu Th - #r Arg **Thr** Ala Val Tyr

50 - # 55 - # 60

- - **Thr** Leu Asn Leu Ala Leu Pro Asp Leu Leu Ty - #r Ala Cys Ser Leu Pro

65 - #. . . #r Ala Asn Leu His Gly

100 - # 105 - # 110

- - Arg Ile Leu Phe Leu **Thr** Cys Ile Ser Phe Gl - #n Arg Tyr Leu Gly Ile

115 - # 120 - # 125

-. . . # 135 - # 140

- - Trp Leu Val Cys Val Ala Val Trp Leu Ala Va - #l **Thr Thr** Gln Cys Leu

145 1 - #50 1 - #55 1 - #60

- - Pro **Thr** Ala Ile Phe Ala Ala **Thr** Gly Ile Gl - #n Arg Asn Arg **Thr** Val

165 - # 170 - # 175

- - Cys Tyr Asp Leu Ser Pro Pro Ala Leu Ala Th. . . - #r His Tyr Met Pro Tyr

180 - # 185 - # 190

- - Gly Met Ala Leu **Thr** Val Ile Gly Phe Leu Le - #u Pro Phe Ala Ala Leu

195 - # 200 - # 205

. . . Phe Gly Ile Se - #r Phe Leu Pro Phe His

245 - # 250 - # 255

- - Ile **Thr** Lys **Thr** Ala Tyr Leu Ala Val Arg Se - #r **Thr** Pro Gly Val Pro

260 - # 265 - # 270

- - Cys **Thr** Val Leu Glu Ala Phe Ala Ala Ala Ty - #r Lys Gly **Thr** Arg Pro

275 - # 280 - # 285

- - Phe Ala Ser Ala Asn Ser Val Leu Asp Pro Il - #e Leu Phe Tyr Phe **Thr**

290 - # 295 - # 300

- - Gln Lys Lys Phe Arg Arg Arg Pro His Glu Le - #u Leu Gln Lys Leu

Thr
305 3 - #10 3 - #15 3 - #20
- - Asp Lys Trp Gln Arg Gln Gly Arg
325

CLM What is claimed is:
. . . synthesis in an outward manner under PCR conditions, and wherein the first primer is capable of being extended in an **antisense** direction and the second primer is capable of being extended in a sense direction; and b) combining said first and. . .

=> d history

(FILE 'HOME' ENTERED AT 13:53:01 ON 04 DEC 2002)

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL, BIOSIS' ENTERED AT 13:53:17 ON 04 DEC 2002

```
L1         82751 S THR OR F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN R
L2          8539 S L1 AND (ANTISENSE OR RIBOZYME OR TRIPLEX)
L3           587 S L1 (P) (ANTISENSE OR RIBOZYME OR TRIPLEX)
L4          7436 S F2R OR (COAGULATION FACTOR II RECEPTOR) OR (THROMBIN RECEPTOR
L5           272 S L4 AND (ANTISENSE OR RIBOZYME OR TRIPLEX)
L6           212 DUP REM L5 (60 DUPLICATES REMOVED)
L7            83 S L6 AND PY<2000
L8          2888 S L2 AND (PLACENTA OR IMPLANTATION)
L9          1989 S L2 AND (PLACENTA)
L10          439 S L2 AND (PLACENTA AND IMPLANTATION)
L11          436 DUP REM L10 (3 DUPLICATES REMOVED)
L12           63 S L11 AND PY<2000
```

```
=> s l6 and (placenta or implantation)
L13           70 L6 AND (PLACENTA OR IMPLANTATION)

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14           70 DUP REM L13 (0 DUPLICATES REMOVED)

=> d l14 ibib abs 1-30

L14  ANSWER 1 OF 70  USPATFULL
ACCESSION NUMBER:         2002:308355  USPATFULL
TITLE:                    Regulation of vascular endothelium using BMX tyrosine
                          kinase
INVENTOR(S):              Ekman, Niklas, Helsinki, FINLAND
                          Arighi, Elena, Helsinki, FINLAND
                          Vastrik, Imre, London, UNITED KINGDOM
                          Tamagnone, Luca, Torino, ITALY
                          Alitalo, Kari, Espoo, FINLAND

                               NUMBER         KIND    DATE
                          ---------------- ------ --------
PATENT INFORMATION:       US 2002173481      A1   20021121
APPLICATION INFO.:        US 2002-186399     A1   20020701  (10)
RELATED APPLN. INFO.:     Continuation of Ser. No. US 2000-538445, filed on 29
                          Mar 2000, PENDING Continuation of Ser. No. US
                          1998-104863, filed on 25 Jun 1998, ABANDONED
                          Continuation-in-part of Ser. No. US 1994-320432, filed
                          on 7 Oct 1994, ABANDONED
DOCUMENT TYPE:            Utility
FILE SEGMENT:             APPLICATION
LEGAL REPRESENTATIVE:     David A. Gass, MARSHALL, GERSTEIN & BORUN, Sears Tower,
                          233 S. Wacker Drive, Suite 6300, Chicago, IL,
                          60606-6357
```

NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 1184

AB Vascular endothelia are subject to atherosclerotic and arteriostenotic effects transduced by molecules, such as thrombin, IL-3 and VEGF which can lead to vessel occlusion or stenosis. An endothelial signaling pathway involving the Bmx tyrosine kinase contributes to normal endothelial nonthrombogenic, inflammatory and growth conditions of arterial vessels, and regulation of the pathway can treat or prevent pathological conditions in the vessel walls.

L14 ANSWER 2 OF 70 USPATFULL

ACCESSION NUMBER: 2002:307870 USPATFULL
TITLE: 28 human secreted proteins
INVENTOR(S): Ruben, Steven M., Olney, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Zeng, Zhizhen, Lansdale, PA, UNITED STATES
Kyaw, Hla, Frederick, MD, UNITED STATES
Fischer, Carrie L., Burke, VA, UNITED STATES
Li, Haodong, Gaithersburg, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
Gentz, Reiner L., Rockville, MD, UNITED STATES
Wei, Ying-Fei, Berkeley, CA, UNITED STATES
Moore, Paul A., Germantown, MD, UNITED STATES
Young, Paul E., Gaithersburg, MD, UNITED STATES
Greene, John M., Gaithersburg, MD, UNITED STATES
Ferrie, Ann M., Tewksbury, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002172994	A1	20021121
APPLICATION INFO.:	US 2001-852797	A1	20010511 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-152060, filed on 11 Sep 1998, PENDING Continuation-in-part of Ser. No. WO 1998-US4858, filed on 12 Mar 1998, UNKNOWN

PRIORITY INFORMATION:	NUMBER	DATE
	US 2001-265583P	20010202 (60)
	US 1997-40762P	19970314 (60)
	US 1997-40710P	19970314 (60)
	US 1997-50934P	19970530 (60)
	US 1997-48100P	19970530 (60)
	US 1997-48357P	19970530 (60)
	US 1997-48189P	19970530 (60)
	US 1997-57765P	19970905 (60)
	US 1997-48970P	19970606 (60)
	US 1997-68368P	19971219 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 17794

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

L14 ANSWER 3 OF 70 USPATFULL
ACCESSION NUMBER: 2002:307817 USPATFULL
TITLE: Methods and reagents for isolating biologically active peptides
INVENTOR(S): Gyuris, Jeno, Winchester, MA, UNITED STATES
Morris, Aaron J., Boston, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002172940	A1	20021121
APPLICATION INFO.:	US 2002-80854	A1	20020222 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-174943, filed on 19 Oct 1998, GRANTED, Pat. No. US 6420110
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624
NUMBER OF CLAIMS: 79
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 3210
AB One aspect of the present invention is the synthesis of a binary method that combines variegated peptide display libraries, e.g., in a "display mode", with soluble secreted peptide libraries, e.g., in a "secretion mode", to yield a method for the efficient isolation of peptides having a desired biological activity.

L14 ANSWER 4 OF 70 USPATFULL
ACCESSION NUMBER: 2002:301210 USPATFULL
TITLE: DNA encoding the human serine protease T
INVENTOR(S): Darrow, Andrew, Lansdale, PA, UNITED STATES
Qi, Jenson, Branchburg, NJ, UNITED STATES
Andrade-Grodon, Patricia, Doylestown, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002168754	A1	20021114
APPLICATION INFO.:	US 2002-41006	A1	20020107 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-386653, filed on 31 Aug 1999, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Philip S. Johnson, Esq., Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ, 08933-7003
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 2046
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Here we describe the molecular identification of a cDNA encoding a novel serine protease we have termed protease T. The deduced amino acid sequence encodes a prepro form of 290 amino acids, and its alignment with other well-characterized serine proteases indicates that it is a member of the S1 serine protease family. We have found that the protease T mRNA is expressed in stomach, testis, retina, fibroblasts, spinal cord, and several regions of the brain. Protease T mRNA is also found in leukocytes and in the Jurkat (ATCC TIB-152) T cell line. Thus, this protease is potentially involved in gastric, testicular, retinal, dematological, neurological/neurodegenerative and/or immunological disorders. The protease T gene maps to human chromosome 16p13.3 which is near the tryptase locus. Enzymatically active protease T, we have generated, is amenable to further biochemical analyses for the

identification of physiological substrates and specific modulators.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 5 OF 70 USPATFULL

ACCESSION NUMBER: 2002:294724 USPATFULL
TITLE: DNA encoding the human serine protease C-E
INVENTOR(S): Darrow, Andrew, Lansdale, PA, UNITED STATES
Qi, Jenson, Branchburg, NJ, UNITED STATES
Andrade-Grodon, Patricia, Doylestown, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002164767	A1	20021107
APPLICATION INFO.:	US 2002-40803	A1	20020107 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-386629, filed on 31 Aug 1999, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Philip S. Johnson, Esq., Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ, 08933-7003
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 2065
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Here we describe the molecular identification of a cDNA encoding a novel serine protease we have termed protease C-E. The deduced amino acid sequence, and it alignment with other well-characterized serine proteases indicates that it is a member of the S1 serine protease family. We have found that the protease C-E mRNA is expressed in pancreas, **placenta**, prostate, small intestine, stomach, spleen, fibroblasts and epidermis, as well as in certain regions of the brain i.e., cerebellum, cerebral cortex, pituitary and hippocampus. Enzymatically active protease C-E, as produced using the methodologies described herein, is amenable to further biochemical analyses for the identification of physiological substrates and specific modulators.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 6 OF 70 USPATFULL

ACCESSION NUMBER: 2002:294294 USPATFULL
TITLE: Bifunctional molecules and vectors complexed therewith for targeted gene delivery
INVENTOR(S): Nemerow, Glen R., Encinitas, CA, UNITED STATES
Li, Erguang, San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S): The Scripps Research Institute (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002164333	A1	20021107
APPLICATION INFO.:	US 2001-903327	A1	20010710 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-325781P	20000710 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STEPHANIE SEIDMAN, HELLER EHRMAN WHITE & MCAULIFFE LLP, 4350 LA JOLLA VILLAGE DRIVE, 7th FL., SAN DIEGO, CA, 92122-1246
NUMBER OF CLAIMS: 39
EXEMPLARY CLAIM: 1
LINE COUNT: 3999
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and products for targeting delivery vectors, such as adenoviral gene delivery particles, to selected cell types are provided. The methods rely on targeting by a bifunctional molecule that specifically complexes with a protein on the vector particle surface and with targeted cell surface proteins. The targeted cell surface proteins are any that activate the phosphatidylinositol-3-OH kinases. The bifunctional molecules, compositions, kits, and methods of preparation and use of the vector/bifunctional molecules for gene therapy are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 7 OF 70 USPATFULL

ACCESSION NUMBER:	2002:280092 USPATFULL		
TITLE:	Regulation of human CysLT2-like GPCR protein		
INVENTOR(S):	Xiao, Yonghong, Cambridge, MA, UNITED STATES		

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002155528	A1	20021024	
APPLICATION INFO.:	US 2001-828478	A1	20010409	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-195196P	20000407	(60)
	US 2000-254876P	20001213	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100, WASHINGTON, DC, 20001
NUMBER OF CLAIMS:	61
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	19 Drawing Page(s)
LINE COUNT:	3518

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Reagents which regulate human CysLT2-like GPCR protein and reagents which bind to human CysLT2-like GPCR gene products can play a role in preventing, ameliorating, or correcting dysfunctions or diseases including, but not limited to peripheral and central nervous system disease, asthma and cardiovascular disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 8 OF 70 USPATFULL

ACCESSION NUMBER:	2002:265929 USPATFULL
TITLE:	DNA encoding the human serine protease T
INVENTOR(S):	Darrow, Andrew, Lansdale, PA, UNITED STATES Qi, Jenson, Branchburg, NJ, UNITED STATES Andrade-Grodon, Patricia, Doylestown, PA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002146805	A1	20021010	
APPLICATION INFO.:	US 2002-40655	A1	20020107	(10)
RELATED APPLN. INFO.:	Division of Ser. No. US 1999-386653, filed on 31 Aug 1999, PENDING			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	Philip S. Johnson, Esq., Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ, 08933-7003			
NUMBER OF CLAIMS:	27			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	6 Drawing Page(s)			
LINE COUNT:	2049			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Here we describe the molecular identification of a cDNA encoding a novel serine protease we have termed protease T. The deduced amino acid sequence encodes a prepro form of 290 amino acids, and its alignment with other well-characterized serine proteases indicates that it is a member of the S1 serine protease family. We have found that the protease T mRNA is expressed in stomach, testis, retina, fibroblasts, spinal cord, and several regions of the brain. Protease T mRNA is also found in leukocytes and in the Jurkat (ATCC TIB-152) T cell line. Thus, this protease is potentially involved in gastric, testicular, retinal, dematological, neurological/neurodegenerative and/or immunological disorders. The protease T gene maps to human chromosome 16p13.3 which is near the tryptase locus. Enzymatically active protease T, we have generated, is amenable to further biochemical analyses for the identification of physiological substrates and specific modulators.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 9 OF 70 USPATFULL
ACCESSION NUMBER: 2002:258714 USPATFULL
TITLE: Methods of identifying renal protective factors
INVENTOR(S): Raha, Debasish, New Haven, CT, UNITED STATES
Green, Cyndi D., Madison, CT, UNITED STATES
Cate, Richard L., Weston, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002142284	A1	20021003	
APPLICATION INFO.:	US 2001-905325	A1	20010713	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-217932P	20000713 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MINTZ, LEVIN, COHN, FERRIS,, GLOVSKY AND POPEO, P.C., One Financial Center, Boston, MA, 02111
NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1
LINE COUNT: 2754
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are methods of identifying toxic agents, e.g., renal toxic agents, using differential gene expression. Also disclosed are novel nucleic acid sequences whose expression is differentially regulated by renal injury agents.

This application claims priority to U.S. Pat. No. b 60/217,932, filed July 13, 2000 which is incorporated herein by reference in its entirety

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 10 OF 70 USPATFULL
ACCESSION NUMBER: 2002:243784 USPATFULL
TITLE: VEGF-modulated genes and methods employing them
INVENTOR(S): Gerber, Hans-Peter, San Francisco, CA, UNITED STATES
Rastelli, Luca, Guilford, CT, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002132978	A1	20020919	
APPLICATION INFO.:	US 2001-815153	A1	20010321	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-191201P	20000322 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BRINKS HOFER GILSON & LIONE, P.O. Box 10395, Chicago, IL, 60610
NUMBER OF CLAIMS: 61
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 5514
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides methods for modulating angiogenesis and/or apoptosis comprising modulating the activity of at least one VEGF-modulated gene polypeptide. The invention also provides pharmaceutical compositions for modulating angiogenesis and apoptosis for the prevention or treatment of diseases associated with VEGF-modulated genes expression. The invention also provides diagnostic assays that use VEGF-modulated gene polynucleotides that hybridize with naturally occurring sequences encoding VEGF-modulated genes and antibodies that specifically bind to the protein.

The invention also provides novel human and mouse arginine-rich proteins (ARPs) and nucleotide sequences. The invention provides for genetically engineered expression vectors and host cells comprising the nucleic acid sequence encoding ARPs and for a method for producing the protein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 11 OF 70 USPATFULL
ACCESSION NUMBER: 2002:235513 USPATFULL
TITLE: Methods and compositions for regulating cell cycle progression
INVENTOR(S): Bernstein, Harold S., San Francisco, CA, UNITED STATES
Coughlin, Shaun R., Tiburon, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002127702	A1	20020912
APPLICATION INFO.:	US 2001-757049	A1	20010108 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-156316, filed on 18 Sep 1998, GRANTED, Pat. No. US 6183961

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-60688P	19970922 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: COOLEY GODWARD LLP, Attention: Patent Group, Five Palo Alto Square, 3000 El Camino Real, Palo Alto, CA, 94306-2155
NUMBER OF CLAIMS: 65
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 21 Drawing Page(s)
LINE COUNT: 3521
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Method and compositions for regulating cell cycle progression are disclosed. Compositions include nucleic acids comprising a human Cdc5 gene, **antisense** gene and fragments thereof and a human Cdc5 protein and polypeptide fragments thereof polypeptide. The consensus DNA binding site for hCdc5 has been described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 12 OF 70 USPATFULL
ACCESSION NUMBER: 2002:213791 USPATFULL
TITLE: Isolation of drosophila and human polynucleotides encoding **PAR-1** kinase, polypeptides encoded by the polynucleotides and methods utilizing

the polynucleotides and polypeptides

INVENTOR(S): Sun, Tian-Qiang, San Francisco, CA, UNITED STATES
Feng, Jia-Jia, San Francisco, CA, UNITED STATES
Reinhard, Christoph, Alameda, CA, UNITED STATES
Fantl, Wendy J., San Francisco, CA, UNITED STATES
Williams, Lewis T., Mill Valley, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002115167	A1	20020822	
APPLICATION INFO.:	US 2001-919585	A1	20010730	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-221860P	20000728 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Chiron Corporation, Intellectual Property R338, P.O. Box 8097, Emeryville, CA, 94662-8097
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
LINE COUNT: 11068
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated nucleic acid molecules comprising polynucleotide having sequences that encode human and Drosophila **PAR-1** kinases. Also provided are proteins and polypeptides encoded by the nucleic acid molecules, methods of modulating **PAR-1** expression and function, and methods of modulating the Wnt signaling pathway.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 13 OF 70 USPATFULL
ACCESSION NUMBER: 2002:206605 USPATFULL
TITLE: Novel nucleic acids and polypeptides
INVENTOR(S): Tang, Y. Tom, San Jose, CA, UNITED STATES
Zhou, Ping, Cupertino, CA, UNITED STATES
Goodrich, Ryle, San Jose, CA, UNITED STATES
Liu, Chenghua, San Jose, CA, UNITED STATES
Asundi, Vinod, Foster City, CA, UNITED STATES
Wang, Jian-Rui, Cupertino, CA, UNITED STATES
Wang, Dunrui, Poway, CA, UNITED STATES
Yamazaki, Victoria, Redwood Shores, CA, UNITED STATES
Ujwal, Manusha L., Gaithersburg, MD, UNITED STATES
Drmanac, Radoje T., Palo Alto, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002111302	A1	20020815	
APPLICATION INFO.:	US 2000-728952	A1	20001130	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Ivor R. Elrifi, Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C, One Financial Center, Boston, MA, 02111
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
LINE COUNT: 4863
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides novel nucleic acids, novel polypeptide sequences encoded by these nucleic acids and uses thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 14 OF 70 USPATFULL
ACCESSION NUMBER: 2002:191522 USPATFULL

TITLE: G protein coupled receptor kinase 5 (GRK5) and its uses
INVENTOR(S): Delaney, Allen, Vancouver, CANADA
Yoganathan, Thillainathan, Richmond, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002102587	A1	20020801
APPLICATION INFO.:	US 2001-972694	A1	20011004 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2001-US21479, filed on 20 Sep 2001, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-237423P	20001002 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PAMELA J. SHERWOOD, Bozicevic, Field and Francis LLP, Suite 200, 200 Middlefield Road, Menlo Park, CA, 94025
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 1356
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Detection of GRK5 expression in cancers is useful as a diagnostic, for determining the effectiveness of drugs, and determining patient prognosis. GRK5 further provides a target for screening pharmaceutical agents effective in inhibiting the growth or metastasis of tumor cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 15 OF 70 USPATFULL
ACCESSION NUMBER: 2002:191154 USPATFULL
TITLE: Diagnostic/therapeutic agents
INVENTOR(S): Klaveness, Jo, Oslo, NORWAY
Rongved, Pal, Oslo, NORWAY
Hogset, Anders, Oslo, NORWAY
Tolleshaug, Helge, Oslo, NORWAY
Cuthbertson, Alan, Oslo, NORWAY
Godal, Aslak, Oslo, NORWAY
Hoff, Lars, Oslo, NORWAY
Gogstad, Geir, Oslo, NORWAY
Bryn, Klaus, Oslo, NORWAY
Naevestad, Anne, Oslo, NORWAY
Lovhaug, Dagfinn, Oslo, NORWAY
Hellebust, Halldis, Oslo, NORWAY
Solbakken, Magne, Oslo, NORWAY
PATENT ASSIGNEE(S): Nycomed Imaging AS (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002102217	A1	20020801
APPLICATION INFO.:	US 2001-925715	A1	20010810 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1997-959206, filed on 28 Oct 1997, PATENTED

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1996-22366	19961028
	GB 1996-22369	19961028
	GB 1997-2195	19970204
	GB 1997-8265	19970424
	GB 1997-11837	19970606
	GB 1997-11839	19970606
	US 1997-49263P	19970607 (60)
	US 1997-49264P	19970606 (60)
	US 1997-49266P	19970607 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Richard E. Fichter, BACON & THOMAS, PLLC, Fourth Floor, 625 Slaters Lane, Alexandria, VA, 22314-1176
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 5190

AB Targetable diagnostic and/or therapeutically active agents, e.g. ultrasound contrast agents, comprising a suspension in an aqueous carrier liquid of a reporter comprising gas-containing or gas-generating material, said agent being capable of forming at least two types of binding pairs with a target.

L14 ANSWER 16 OF 70 USPATFULL
ACCESSION NUMBER: 2002:165193 USPATFULL
TITLE: Nucleic acids, proteins, and antibodies
INVENTOR(S): Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002086822	A1	20020704	
APPLICATION INFO.:	US 2001-764886	A1	20010117	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-179065P	20000131	(60)
	US 2000-180628P	20000204	(60)
	US 2000-214886P	20000628	(60)
	US 2000-217487P	20000711	(60)
	US 2000-225758P	20000814	(60)
	US 2000-220963P	20000726	(60)
	US 2000-217496P	20000711	(60)
	US 2000-225447P	20000814	(60)
	US 2000-218290P	20000714	(60)
	US 2000-225757P	20000814	(60)
	US 2000-226868P	20000822	(60)
	US 2000-216647P	20000707	(60)
	US 2000-225267P	20000814	(60)
	US 2000-216880P	20000707	(60)
	US 2000-225270P	20000814	(60)
	US 2000-251869P	20001208	(60)
	US 2000-235834P	20000927	(60)
	US 2000-234274P	20000921	(60)
	US 2000-234223P	20000921	(60)
	US 2000-228924P	20000830	(60)
	US 2000-224518P	20000814	(60)
	US 2000-236369P	20000929	(60)
	US 2000-224519P	20000814	(60)
	US 2000-220964P	20000726	(60)
	US 2000-241809P	20001020	(60)
	US 2000-249299P	20001117	(60)
	US 2000-236327P	20000929	(60)
	US 2000-241785P	20001020	(60)
	US 2000-244617P	20001101	(60)
	US 2000-225268P	20000814	(60)
	US 2000-236368P	20000929	(60)
	US 2000-251856P	20001208	(60)
	US 2000-251868P	20001208	(60)
	US 2000-229344P	20000901	(60)
	US 2000-234997P	20000925	(60)
	US 2000-229343P	20000901	(60)

US 2000-229345P	20000901	(60)
US 2000-229287P	20000901	(60)
US 2000-229513P	20000905	(60)
US 2000-231413P	20000908	(60)
US 2000-229509P	20000905	(60)
US 2000-236367P	20000929	(60)
US 2000-237039P	20001002	(60)
US 2000-237038P	20001002	(60)
US 2000-236370P	20000929	(60)
US 2000-236802P	20001002	(60)
US 2000-237037P	20001002	(60)
US 2000-237040P	20001002	(60)
US 2000-240960P	20001020	(60)
US 2000-239935P	20001013	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
LINE COUNT: 20931
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 17 OF 70 USPATFULL
ACCESSION NUMBER: 2002:157081 USPATFULL
TITLE: Compositions and methods for the therapy and diagnosis of prostate cancer
INVENTOR(S): Xu, Jiangchun, Bellevue, WA, UNITED STATES
Dillon, Davin C., Issaquah, WA, UNITED STATES
Mitcham, Jennifer L., Redmond, WA, UNITED STATES
Harlocker, Susan L., Seattle, WA, UNITED STATES
Jiang, Yuqiu, Kent, WA, UNITED STATES
Kalos, Michael D., Seattle, WA, UNITED STATES
Fanger, Gary R., Mill Creek, WA, UNITED STATES
Retter, Marc W., Carnation, WA, UNITED STATES
Stolk, John A., Bothell, WA, UNITED STATES
Day, Craig H., Seattle, WA, UNITED STATES
Vedvick, Thomas S., Federal Way, WA, UNITED STATES
Carter, Darrick, Seattle, WA, UNITED STATES
Li, Samuel X., Redmond, WA, UNITED STATES
Wang, Aijun, Issaquah, WA, UNITED STATES
Skeiky, Yasir A. W., Bellevue, WA, UNITED STATES
Hepler, William T., Seattle, WA, UNITED STATES
Henderson, Robert A., Edmonds, WA, UNITED STATES
Hural, John, Bainbridge Island, WA, UNITED STATES
McNeill, Patricia D., Federal Way, WA, UNITED STATES
Houghton, Raymond L., Bothell, WA, UNITED STATES
de Bassols, Carlota Vinals, Rixensart, BELGIUM

NUMBER	KIND	DATE

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002081680	A1	20020627
APPLICATION INFO.:	US 2001-822827	A1	20010328 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-780669, filed on 9 Feb 2001, PENDING Continuation-in-part of Ser. No. US 2000-679272, filed on 4 Oct 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-157455P	20000417 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 7692
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis prevention and/or treatment of diseases, particularly prostate cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 18 OF 70 USPATFULL
ACCESSION NUMBER: 2002:149131 USPATFULL
TITLE: 28 human secreted proteins
INVENTOR(S): Ruben, Steven M., Olney, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Zeng, Zhizhen, Lansdale, PA, UNITED STATES
Kyaw, Hla, Frederick, MD, UNITED STATES
Fischer, Carrie L., Burke, VA, UNITED STATES
Li, Haodong, Gaithersburg, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
Gentz, Reiner L., Rockville, MD, UNITED STATES
Wei, Ying-Fei, Berkeley, CA, UNITED STATES
Moore, Paul A., Germantown, MD, UNITED STATES
Young, Paul E., Gaithersburg, MD, UNITED STATES
Greene, John M., Gaithersburg, MD, UNITED STATES
Ferrie, Ann M., Tewksbury, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002077287	A1	20020620
APPLICATION INFO.:	US 2001-852659	A1	20010511 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-152060, filed on 11 Sep 1998, UNKNOWN
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 17779
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells,

antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 19 OF 70 USPATFULL

ACCESSION NUMBER: 2002:148614 USPATFULL
TITLE: 28 human secreted proteins
INVENTOR(S): Ruben, Steven M., Olney, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Zeng, ZhiZhen, Lansdale, PA, UNITED STATES
Kyaw, Hla, Frederick, MD, UNITED STATES
Fischer, Carrie L., Burke, VA, UNITED STATES
Li, Haodong, Gaithersburg, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
Gentz, Reiner L., Rockville, MD, UNITED STATES
Wei, Ying-Fei, Berkeley, CA, UNITED STATES
Moore, Paul A., Germantown, MD, UNITED STATES
Young, Paul E., Gaithersburg, MD, UNITED STATES
Greene, John M., Gaithersburg, MD, UNITED STATES
Ferrie, Ann M., Painted Post, NY, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002076756	A1	20020620	
APPLICATION INFO.:	US 2001-853161	A1	20010511	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-265583P	20010202 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 17788
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 20 OF 70 USPATFULL

ACCESSION NUMBER: 2002:148613 USPATFULL
TITLE: G protein coupled receptor (GPCR) agonists and antagonists and methods of activating and inhibiting GPCR using the same
INVENTOR(S): Kuliopulos, Athan, Winchester, MA, UNITED STATES
Covic, Lidija, Boston, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002076755	A1	20020620	
APPLICATION INFO.:	US 2001-841091	A1	20010423	(9)

	NUMBER	DATE

PRIORITY INFORMATION:	US 2000-198993P	20000421 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Ivor R. Elrifi, Esq., MINTZ, LEVIN, COHN, FERRIS,, GLOVSKY and POPEO, P.C., One Financial Center, Boston, MA, 02111	
NUMBER OF CLAIMS:	34	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	20 Drawing Page(s)	
LINE COUNT:	1904	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates generally to G protein coupled receptors and in particular to agonists and antagonists of G protein receptors and methods of using the same.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 21 OF 70 USPATFULL

ACCESSION NUMBER:	2002:105925 USPATFULL		
TITLE:	Method and product for regulating apoptosis		
INVENTOR(S):	Johnson, Gary L., Boulder, CO, UNITED STATES		
PATENT ASSIGNEE(S):	National Jewish Center for Immunology and Respiratory Medicine (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002055130	A1	20020509
APPLICATION INFO.:	US 2001-858754	A1	20010516 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1998-23130, filed on 13 Feb 1998, ABANDONED		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-39740P	19970214 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109	
NUMBER OF CLAIMS:	39	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	22 Drawing Page(s)	
LINE COUNT:	6845	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to isolated MEKK1 proteins, nucleic acid molecules having sequences that encode such proteins, and antibodies raised against such proteins. The present invention also includes methods to use such proteins to regulate apoptosis. The invention provides active fragments of MEKK1 proteins that are generated upon cleavage of MEKK1 with a caspase protease. These active fragments are capable of stimulating apoptosis. Moreover, the invention provides protease-resistant forms of MEKK1 proteins, that are resistant to cleavage by caspase proteases and that are capable of inhibiting apoptosis. Still further, the invention provides methods for generating an active fragment of MEKK1, methods of identifying modulators of the apoptotic activity of an active fragment of MEKK1 and methods of identifying modulators of caspase-mediated cleavage of MEKK1.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 22 OF 70 USPATFULL

ACCESSION NUMBER:	2002:99081 USPATFULL
TITLE:	Compositions and methods for the therapy and diagnosis of prostate cancer
INVENTOR(S):	Xu, Jiangchun, Bellevue, WA, UNITED STATES Dillon, Davin C., Issaquah, WA, UNITED STATES

Mitcham, Jennifer L., Redmond, WA, UNITED STATES
Harlocker, Susan L., Seattle, WA, UNITED STATES
Jiang, Yuqiu, Kent, WA, UNITED STATES
Kalos, Michael D., Seattle, WA, UNITED STATES
Fanger, Gary R., Mill Creek, WA, UNITED STATES
Retter, Marc W., Carnation, WA, UNITED STATES
Stolk, John A., Bothell, WA, UNITED STATES
Day, Craig H., Seattle, WA, UNITED STATES
Vedvick, Thomas S., Federal Way, WA, UNITED STATES
Carter, Darrick, Seattle, WA, UNITED STATES
Li, Samuel X., Redmond, WA, UNITED STATES
Wang, Aijun, Issaquah, WA, UNITED STATES
Skeiky, Yasir A. W., Bellevue, WA, UNITED STATES
Hepler, William T., Seattle, WA, UNITED STATES
Henderson, Robert A., Edmonds, WA, UNITED STATES
Hural, John, Bainbridge Island, WA, UNITED STATES
McNeill, Patricia D., Des Moines, WA, UNITED STATES
Houghton, Raymond L., Bothell, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002051977	A1	20020502
APPLICATION INFO.:	US 2001-780669	A1	20010209 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-759143, filed on 12 Jan 2001, PENDING Continuation-in-part of Ser. No. US 2000-709729, filed on 9 Nov 2000, PENDING Continuation-in-part of Ser. No. US 2000-685166, filed on 10 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-679426, filed on 2 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-657279, filed on 6 Sep 2000, PENDING Continuation-in-part of Ser. No. US 2000-651236, filed on 29 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-636215, filed on 10 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-605783, filed on 27 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-593793, filed on 13 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-510737, filed on 1 May 2000, GRANTED, Pat. No. US 6219981 Continuation-in-part of Ser. No. US 2000-568100, filed on 9 May 2000, PENDING Continuation-in-part of Ser. No. US 2000-536857, filed on 27 Mar 2000, PENDING Continuation-in-part of Ser. No. US 2000-483672, filed on 14 Jan 2000, PENDING Continuation-in-part of Ser. No. US 1999-443686, filed on 18 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-439313, filed on 12 Nov 1999, PENDING Continuation-in-part of Ser. No. US 1999-352616, filed on 13 Jul 1999, PENDING Continuation-in-part of Ser. No. US 1999-288946, filed on 9 Apr 1999, PENDING Continuation-in-part of Ser. No. US 1999-232149, filed on 15 Jan 1999, PENDING Continuation-in-part of Ser. No. US 1998-159812, filed on 23 Sep 1998, PENDING Continuation-in-part of Ser. No. US 1998-115453, filed on 14 Jul 1998, PENDING Continuation-in-part of Ser. No. US 1998-30607, filed on 25 Feb 1998, GRANTED, Pat. No. US 6262245 Continuation-in-part of Ser. No. US 1998-20956, filed on 9 Feb 1998, GRANTED, Pat. No. US 6261562 Continuation-in-part of Ser. No. US 1997-904804, filed on 1 Aug 1997, ABANDONED Continuation-in-part of Ser. No. US 1997-806099, filed on 25 Feb 1997, ABANDONED Continuation-in-part of Ser. No. WO 1998-US3492, filed on 25 Feb 1998, UNKNOWN Continuation-in-part of Ser. No. WO 1999-US15838, filed on 14 Jul 1999, UNKNOWN

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 7556
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly prostate cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 23 OF 70 USPATFULL
ACCESSION NUMBER: 2002:92054 USPATFULL
TITLE: Chimeric polypeptides of serum albumin and uses related thereto
INVENTOR(S): Gyuris, Jeno, Winchester, MA, UNITED STATES
Lamphere, Lou, Newton, MA, UNITED STATES
Morris, Aaron, Brighton, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002048571	A1	20020425
APPLICATION INFO.:	US 2001-768183	A1	20010123 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-764918, filed on 18 Jan 2001, PENDING Continuation-in-part of Ser. No. US 2000-619285, filed on 19 Jul 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-144534P	19990719 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Page(s)
LINE COUNT: 1937
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to chimeric polypeptides in which a serum albumin protein has been altered to include one or more biologically active heterologous peptide sequences. The chimeric polypeptides may exhibit therapeutic activity related to the heterologous peptide sequences coupled with the improved serum half-lives derived from the serum albumin protein fragments. Heterologous peptide sequences maybe chosen to promote any biological effect, including angiogenesis inhibition, antitumor activity, and induction of apoptosis. The therapeutic effect may be achieved by direct administration of the chimeric polypeptide, or by transfecting cells with a vector including a nucleic acid encoding such a chimeric polypeptide.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 24 OF 70 USPATFULL
ACCESSION NUMBER: 2002:85547 USPATFULL
TITLE: Hirulog-like peptide and gene therapy
INVENTOR(S): Shen, Gary, Winnipeg, CANADA

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002045589	A1	20020418	
APPLICATION INFO.:	US 2001-822882	A1	20010330	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-193114P	20000330 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KOHN & ASSOCIATES, 30500 Northwestern Highway, Suite 410, Farmington Hills, MI, 48334
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 2150
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There is provided a hirulog-like peptide. Also provided is the treatment of vascular restenosis including the steps of administering an effective amount of a hirulog-like peptide in a pharmaceutically acceptable carrier whereby administration prevents vascular restenosis. A pharmaceutical composition including a hirulog-like peptide and a pharmaceutically acceptable carrier is also provided. A vector expressing a hirulog-like peptide is also provided. Also provided by the present invention is a method of treating a patient with vascular restenosis by introducing to the patient an amount of a sequence encoding a hirulog-like peptide sufficient to prevent vascular restenosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 25 OF 70 USPATFULL
ACCESSION NUMBER: 2002:72993 USPATFULL
TITLE: Epstein barr virus induced genes
INVENTOR(S): Birkenbach, Mark, Tinley Park, IL, UNITED STATES
Kieff, Elliot, Brookline, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002040133	A1	20020404	
APPLICATION INFO.:	US 2001-929583	A1	20010814	(9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-536954, filed on 28 Mar 2000, PENDING Division of Ser. No. US 1994-352678, filed on 30 Nov 1994, GRANTED, Pat. No. US 6043351 Continuation of Ser. No. US 1992-980518, filed on 25 Nov 1992, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOLF GREENFIELD & SACKS, PC, FEDERAL RESERVE PLAZA, 600 ATLANTIC AVENUE, BOSTON, MA, 02210-2211
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 2122
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates, in general, to Epstein Barr virus induced (EBI) genes. In particular, the present invention relates to DNA segments coding for EBI 1, EBI 2, or EBI 3 polypeptides; EBI 1, EBI 2, or EBI 3 polypeptides; recombinant DNA molecules; cells containing the recombinant DNA molecules; **antisense** EBI 1, EBI 2, or EBI 3 constructs; antibodies having binding affinity to an EBI 1, EBI 2, or EBI 3 polypeptide; hybridomas containing the antibodies; nucleic acid probes for the detection of the presence of Epstein Barr Virus; a method of detecting Epstein Barr virus in a sample; and kits containing nucleic

acid probes or antibodies.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 26 OF 70 USPATFULL

ACCESSION NUMBER: 2002:43170 USPATFULL

TITLE: Methods and reagents for isolating biologically active antibodies

INVENTOR(S): Gyuris, Jeno, Winchester, MA, UNITED STATES
Ewert, Sebastian-Meier, Wolfratshausen, GERMANY, FEDERAL REPUBLIC OF
Nagy, Zolton, Wolfratshausen, GERMANY, FEDERAL REPUBLIC OF
Morris, Aaron, Brighton, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002025536	A1	20020228	
APPLICATION INFO.:	US 2001-891557	A1	20010626	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-214200P	20000626 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624
NUMBER OF CLAIMS: 83
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 3051
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB One aspect of the present invention is the synthesis of a binary method that combines variegated antibody display libraries, e.g., in a "display mode", with soluble secreted antibody libraries, e.g., in a "secretion mode", to yield a method for the efficient isolation of antibodies having a desired biological activity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 27 OF 70 USPATFULL

ACCESSION NUMBER: 2002:37531 USPATFULL

TITLE: Compositions and methods for the therapy and diagnosis of prostate cancer

INVENTOR(S): Xu, Jiangchun, Bellevue, WA, UNITED STATES
Dillon, Davin C., Issaquah, WA, UNITED STATES
Mitcham, Jennifer L., Redmond, WA, UNITED STATES
Harlocker, Susan L., Seattle, WA, UNITED STATES
Jiang, Yuqiu, Kent, WA, UNITED STATES
Kalos, Michael D., Seattle, WA, UNITED STATES
Fanger, Gary R., Mill Creek, WA, UNITED STATES
Retter, Marc W., Carnation, WA, UNITED STATES
Stolk, John A., Bothell, WA, UNITED STATES
Day, Craig H., Seattle, WA, UNITED STATES
Vedvick, Thomas S., Federal Way, WA, UNITED STATES
Carter, Darrick, Seattle, WA, UNITED STATES
Li, Samuel X., Redmond, WA, UNITED STATES
Wang, Aijun, Issaquah, WA, UNITED STATES
Skeiky, Yasir A. W., Bellevue, WA, UNITED STATES
Hepler, William T., Seattle, WA, UNITED STATES
Henderson, Robert A., Edmonds, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002022248	A1	20020221

APPLICATION INFO.: US 2001-759143 A1 20010112 (9)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-685166, filed on 10 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-679426, filed on 2 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-657279, filed on 6 Sep 2000, PENDING Continuation-in-part of Ser. No. US 2000-651236, filed on 29 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-636215, filed on 10 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-605783, filed on 27 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-593793, filed on 13 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-570737, filed on 12 May 2000, PENDING Continuation-in-part of Ser. No. US 2000-568100, filed on 9 May 2000, PENDING Continuation-in-part of Ser. No. US 2000-536857, filed on 27 Mar 2000, PENDING Continuation-in-part of Ser. No. US 2000-483672, filed on 14 Jan 2000, PENDING Continuation-in-part of Ser. No. US 1999-443686, filed on 18 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-439313, filed on 12 Nov 1999, PENDING Continuation-in-part of Ser. No. US 1999-352616, filed on 13 Jul 1999, PENDING Continuation-in-part of Ser. No. US 1999-288946, filed on 9 Apr 1999, PENDING Continuation-in-part of Ser. No. US 1999-232149, filed on 15 Jan 1999, PENDING Continuation-in-part of Ser. No. US 1998-159812, filed on 23 Sep 1998, PENDING Continuation-in-part of Ser. No. US 1998-115453, filed on 14 Jul 1998, PENDING Continuation-in-part of Ser. No. US 1998-30607, filed on 25 Feb 1998, GRANTED, Pat. No. US 6262245 Continuation-in-part of Ser. No. US 1998-20956, filed on 9 Feb 1998, GRANTED, Pat. No. US 6261562 Continuation-in-part of Ser. No. US 1997-904804, filed on 1 Aug 1997, ABANDONED Continuation-in-part of Ser. No. US 1997-806099, filed on 25 Feb 1997, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 7383
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly prostate cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 28 OF 70 USPATFULL
ACCESSION NUMBER: 2002:16850 USPATFULL
TITLE: Human stress array
INVENTOR(S): Chenchik, Alex, Palo Alto, CA, UNITED STATES
Lukashev, Matvey E., Newton, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002009730	A1	20020124	
APPLICATION INFO.:	US 2001-782909	A1	20010213	(9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-441920, filed on 17 Nov 1999, UNKNOWN
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Bret E. Field, BOZICEVIC, FIELD & FRANCIS LLP, 200 Middlefield Road, Suite 200, Menlo Park, CA, 94025
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
LINE COUNT: 2377
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Human stress arrays and methods for their use are provided. The subject arrays include a plurality of polynucleotide spots, each of which is made up of a polynucleotide probe composition of unique polynucleotides corresponding to a human stress gene. The subject arrays find use in hybridization assays, particularly in assays for the identification of differential gene expression of human stress genes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 29 OF 70 USPATFULL
ACCESSION NUMBER: 2002:254200 USPATFULL
TITLE: DNA encoding the human serine protease T
INVENTOR(S): Darrow, Andrew, Lansdale, PA, United States
Qi, Jenson, Branchburg, NJ, United States
Andrade-Grodon, Patricia, Doylestown, PA, United States
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6458564	B1	20021001	
APPLICATION INFO.:	US 1999-386653		19990831	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Achutamurthy, Ponnathapu
ASSISTANT EXAMINER: Moore, William W.
LEGAL REPRESENTATIVE: Wallen, III, John W.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 2073
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Here we describe the molecular identification of a cDNA encoding a novel serine protease we have termed protease T. The deduced amino acid sequence encodes a prepro form of 290 amino acids, and its alignment with other well-characterized serine proteases indicates that it is a member of the S1 serine protease family. We have found that the protease T mRNA is expressed in stomach, testis, retina, fibroblasts, spinal cord, and several regions of the brain. Protease T MRNA is also found in leukocytes and in the Jurkat (ATCC TIB-152) T cell line. Thus, this protease is potentially involved in gastric, testicular, retinal, dematological, neurological/neurodegenerative and/or immunological disorders. The protease T gene maps to human chromosome 16p13.3 which is near the tryptase locus. Enzymatically active protease T, we have generated, is amenable to further biochemical analyses for the identification of physiological substrates and specific modulators.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 30 OF 70 USPATFULL
ACCESSION NUMBER: 2002:230959 USPATFULL
TITLE: Testis expressed polypeptide
INVENTOR(S): Ruben, Steven M., Olney, MD, United States
Rosen, Craig A., Laytonsville, MD, United States
Zeng, Zhizhen, Gaithersburg, MD, United States

PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6448230	B1	20020910
APPLICATION INFO.:	US 1998-152060		19980911 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 1998-US4858, filed on 12 Mar 1998

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-40762P	19970314 (60)
	US 1997-40710P	19970314 (60)
	US 1997-50934P	19970530 (60)
	US 1997-48100P	19970530 (60)
	US 1997-48357P	19970530 (60)
	US 1997-48189P	19970530 (60)
	US 1997-57765P	19970905 (60)
	US 1997-48970P	19970606 (60)
	US 1997-68368P	19971219 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Davenport, Avis M.
LEGAL REPRESENTATIVE: Human Genome Sciences Inc.
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 7777
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l14 ibib kwic 1-30

L14 ANSWER 1 OF 70 USPATFULL
ACCESSION NUMBER: 2002:308355 USPATFULL
TITLE: Regulation of vascular endothelium using BMX tyrosine kinase
INVENTOR(S): Ekman, Niklas, Helsinki, FINLAND
Arighi, Elena, Helsinki, FINLAND
Vastrik, Imre, London, UNITED KINGDOM
Tamagnone, Luca, Torino, ITALY
Alitalo, Kari, Espoo, FINLAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002173481	A1	20021121
APPLICATION INFO.:	US 2002-186399	A1	20020701 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-538445, filed on 29 Mar 2000, PENDING Continuation of Ser. No. US 1998-104863, filed on 25 Jun 1998, ABANDONED Continuation-in-part of Ser. No. US 1994-320432, filed on 7 Oct 1994, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: David A. Gass, MARSHALL, GERSTEIN & BORUN, Sears Tower,

233 S. Wacker Drive, Suite 6300, Chicago, IL, 60606-6357
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 1184

SUMM . . . 276:1423-1425; herein incorporated by reference). Thus, the signals mediated through VEGF receptors appear to be cell type specific. The VEGF-related **placenta** growth factor (PlGF) was recently shown to bind to VEGFR-1 with high affinity. PlGF was able to enhance the mitogenic. . .

SUMM . . . is thrombin, which is activated by blood clotting, has strong effects on endothelial cells directly, via an endothelial G-protein coupled **thrombin receptor**, and via platelet activation with the resulting release of effectors from platelet alpha granules.

SUMM [0016] In preferred embodiments, a tyrosine kinase inhibitor or BMX **antisense** cDNA is the agent used to inhibit the Bmx tyrosine kinase activity. Alternatively, genetically modified BMX cDNA is used to. . .

SUMM . . . order to accelerate the re-endothelialization of damage endothelium after surgery in the vessel wall, such as balloon angioplasty or the **implantation** of a vascular prosthesis. By "re-endothelialization is meant the regrowth of healthy endothelial lining of a vessel damaged by disease. . .

SUMM [0023] Terms used herein are to be given their art-known meaning. For example, the term "**antisense**" means an RNA or DNA sequence which is sufficiently complementary to a particular target RNA or DNA molecule for which the **antisense** RNA or DNA is directed to cause molecular hybridization between the **antisense** RNA or DNA and the target RNA or DNA such that transcription or translation of RNA or protein is inhibited. Such hybridization occurs in vivo, that is, inside the cell. The action of the **antisense** molecule results in specific inhibition of gene expression in the cell. (See: Alberts, B. et al., Molecular Biology of the Cell, 2nd Ed., Garland Publishing, Inc., New York. N.Y. (1989), in particular, pages 195-196; herein incorporated by reference.) The **antisense** molecule may be comprised of 10 or more naturally or non-naturally occurring nucleotides (e.g., an example of a non-naturally occurring. . .

DETD . . . can be enhanced by stably or transiently incorporating Bmx DNA or RNA into arterial endothelial cells or decreased by transfecting **antisense** DNA into endothelial cells. The best way, however, to regulate Bmx function is by use of specific tyrosine kinase inhibitors,. . .

DETD . . . sufficient to produce the normal physiological effects of the Bmx protein if that is desired, or to inhibit (e.g., through **antisense**) endogenous production of Bmx. The incorporated genetic material may encode a selectable marker, thus providing a means by which cells. . .

DETD . . . interest not normally expressed at biologically significant levels in endothelial cells. Using, e.g., a retroviral vector, the Bmx mRNA or **antisense** can be controlled by a retroviral promoter. Alternatively, retroviral vectors having additional promoter elements (in addition to the promoter incorporated. . . by activating that external factor or cue. Transduction performed in vivo involves applying the recombinant retrovirus encoding Bmx sense or **antisense** DNA to the desired endothelial cells by, e.g., site directed administration of recombinant retrovirus into a blood vessel via a. . .

DETD [0061] The mouse Bmx **antisense** and sense RNA probes were synthesized from linearized pBluescript II SK+plasmid (Stratagene, La Jolla, Calif.), containing a Hind III-EcoRI fragment. . .

DETD . . . (1995) Seminars in Immnunology 7:237-246; Miyazoto et al., (1996) Cell Growth and Differentiation 7:1135-1139; herein incorporated by reference). In addition, **thrombin receptor**, which is coupled to G-protein mediated signal transduction was shown to

stimulate phosphorylation of the Tec kinase related to Bmx. . .

CLM What is claimed is:

6. The method of claim 3 wherein the agent comprises **antisense** BMX cDNA.

18. The method of claim 6 wherein the **antisense** BMX cDNA comprises a promoter operably linked to the **antisense** cDNA.

L14 ANSWER 2 OF 70 USPATFULL

ACCESSION NUMBER: 2002:307870 USPATFULL

TITLE: 28 human secreted proteins

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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002172994	A1	20021121
APPLICATION INFO.:	US 2001-852797	A1	20010511 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-152060, filed on 11 Sep 1998, PENDING Continuation-in-part of Ser. No. WO 1998-US4858, filed on 12 Mar 1998, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-265583P	20010202 (60)
	US 1997-40762P	19970314 (60)
	US 1997-40710P	19970314 (60)
	US 1997-50934P	19970530 (60)
	US 1997-48100P	19970530 (60)
	US 1997-48357P	19970530 (60)
	US 1997-48189P	19970530 (60)
	US 1997-57765P	19970905 (60)
	US 1997-48970P	19970606 (60)
	US 1997-68368P	19971219 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

NUMBER OF CLAIMS: 23

EXEMPLARY CLAIM: 1

LINE COUNT: 17794

SUMM [0037] This gene is expressed primarily in **placenta**, and to a lesser extent, in T-cells.

SUMM . . . this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g.immune, hematopoietic, **placenta**, and T-cells, and cancerous and wounded tissues) or bodily fluids (e.g.lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal. . .

SUMM [0113] The translation product of this gene shares sequence homology with a frog **thrombin receptor** [Xenopus laevis]. Moreover, another group recently cloned this same gene, also recognizing the homology to thrombing receptors. (See Accession NO:. . .

SUMM . . . effects. Additionally, neovascularization and various cell-type specific proliferation effects have been seen. The fact that this clone was isolated from **placenta** RNA may make this an interesting gene to characterize. The known neurokinins are expressed in either the central nervous system. . .

SUMM [0129] This gene is expressed primarily in human **placenta** and to a lesser extent in soares **placenta**.

SUMM . . . of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., **placenta**, and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine,. . .

SUMM [0183] This gene is expressed primarily in the testes and to a lesser extent in the lung, tonsils, **placenta**, and rhabdomyosarcoma.

SUMM . . . for diagnosis of diseases and conditions which include, but are not limited to, diseases related to the testes, lung, tonsils, **placenta**, and tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of. . . a number of disorders of the above tissues or cells, particularly of the diseases related to the testes, lung, tonsils, **placenta**, and tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., testes and other reproductive tissue, lung, tonsils, **placenta**, and striated muscle, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, serum, plasma, urine, synovial fluid or. . .

SUMM . . . and polypeptides corresponding to the gene are useful for diagnosis and treatment of diseases related to the testes, lung, tonsils, **placenta**, and tumors. More specifically, the tissue distribution indicates that the protein product of this clone is useful for the treatment. . .

SUMM [0201] This gene is expressed primarily in **placenta** and human amygdala, and to a lesser extent in adult brain, primary dendritic cells, keratinocytes, activated monocytes, human cerebellum, and. . .

SUMM . . . of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., **placenta**, amygdala, brain and other tissue of the nervous system, dendritic cells, blood cells, keratinocytes, and cancerous and wounded tissues) or. . .

SUMM [0465] In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or **antisense** DNA or RNA. **Antisense** techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRCPress, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance Lee et al.,. . . (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (**antisense**--Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while **antisense** RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design **antisense** or triple helix polynucleotides in an effort to treat or prevent disease.

SUMM . . . or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and **antisense** DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires. . .

SUMM [0598] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, **antisense** nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example. . .

SUMM . . . telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo **implantation** controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter. . .

SUMM [0701] In one aspect of the birth control method, an amount of the compound sufficient to block embryo **implantation** is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a. . . and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal **implantation** in the treatment of endometriosis.

SUMM . . . abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, **placenta** previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the. . .

SUMM . . . into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., **antisense** or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and. . .

SUMM [0842] **Antisense** and **Ribozyme** (Antagonists)

SUMM . . . in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, **antisense** sequence is generated internally by the organism, in another embodiment, the **antisense** sequence is separately administered (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Anitsense Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). **Antisense** technology can be used to control gene expression through **antisense** DNA or RNA, or through triple-helix formation. **Antisense** techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance, Lee et. . .

SUMM [0844] For example, the use of c-myc and c-myb **antisense** RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described.. . . A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given **antisense** RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked. . .

SUMM . . . coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an **antisense** RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The **antisense** RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

SUMM [0846] In one embodiment, the **antisense** nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an **antisense** nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the **antisense** nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired **antisense** RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral,. . .

SUMM [0847] The **antisense** nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a.

. . sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded **antisense** nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or **triplex** formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the **antisense** nucleic acid Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or **triplex** as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of. . .

SUMM . . . to either the 5'- or 3'-non-related, non-coding regions of a polynucleotide sequence of the invention could be used in an **antisense** approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. **Antisense** oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA, **antisense** nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50. . .

SUMM [0850] The **antisense** oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to,. . .

SUMM [0851] The **antisense** oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose,. . .

SUMM [0852] In yet another embodiment, the **antisense** oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a. . .

SUMM [0853] In yet another embodiment, the **antisense** oligonucleotide is an a-anomeric oligonucleotide. An a-anomenrc oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the. . .

SUMM [0855] While **antisense** nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated region. . .

SUMM [0856] Potential antagonists according to the invention also include catalytic RNA, or a **ribozyme** (See, e.g., PCT International Publication WO 90/11364, published Oct. 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While ribozymes that. . . in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead **ribozyme** cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the **ribozyme** is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the. . .

SUMM [0857] As in the **antisense** approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the **ribozyme** may be introduced into the cell in the same manner as described above for the introduction of **antisense** encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the **ribozyme** under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the **ribozyme** to destroy endogenous messages and inhibit translation. Since ribozymes unlike **antisense** molecules, are catalytic, a lower intracellular concentration is required for efficiency.

SUMM . . . throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient

(a) an **antisense** molecule directed to the polynucleotide of the present invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention. invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention.

DETD . . . that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, **antisense**.

DETD . . . and which may be administered in combination with the compositons of the invention include, but are not limited to, Angiozyme (**Ribozyme**, Boulder, Colo.), Anti-VEGF antibody (Genentech, S. San Francisco, Calif.), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, Calif.), SU-5416. . .

DETD [1179] In one example, **antisense** technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a. . . of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously **antisense** polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the **antisense** polynucleotide is provided in Example 23.

DETD . . . treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and **antisense** DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the. . .

L14 ANSWER 3 OF 70 USPATFULL

ACCESSION NUMBER: 2002:307817 USPATFULL

TITLE: Methods and reagents for isolating biologically active peptides

INVENTOR(S): Gyuris, Jeno, Winchester, MA, UNITED STATES
Morris, Aaron J., Boston, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002172940	A1	20021121
APPLICATION INFO.:	US 2002-80854	A1	20020222 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-174943, filed on 19 Oct 1998, GRANTED, Pat. No. US 6420110

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624

NUMBER OF CLAIMS: 79

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 14 Drawing Page(s)

LINE COUNT: 3210

DETD . . . example, angiogenesis is normally observed in wound healing. fetal and embryonal development and formation of the corpus luteum, endometrium and **placenta**. The term "endothelium" means a thin layer of flat epithelial cells that lines serous cavities, lymph vessels, and blood vessels.. . .

DETD . . . beneficial gene. Repression may be achieved by operably linking a receptor- induced promoter to a gene encoding mRNA which is **antisense** to at least a portion of the mRNA encoded by the marker gene (whether in the coding or flanking regions),. . .

DETD . . . substance K (neurokinin A) receptor, fMLP receptor, fMLP-like receptor, angiotensin II type 1 receptor, endothelin ETA receptor, endothelin ETB receptor, **thrombin receptor**, growth hormone-releasing hormone (GHRH) receptor, vasoactive intestinal peptide receptor, oxytocin receptor, somatostatin SSTR1 and SSTR2, SSTR3, cannabinoid receptor, follicle stimulating. . .

L14 ANSWER 4 OF 70 USPATFULL

ACCESSION NUMBER:	2002:301210 USPATFULL
TITLE:	DNA encoding the human serine protease T
INVENTOR(S):	Darrow, Andrew, Lansdale, PA, UNITED STATES Qi, Jenson, Branchburg, NJ, UNITED STATES Andrade-Grodon, Patricia, Doylestown, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002168754	A1	20021114
APPLICATION INFO.:	US 2002-41006	A1	20020107 (10)

RELATED APPLN. INFO.:	Division of Ser. No. US 1999-386653, filed on 31 Aug 1999, PENDING
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Philip S. Johnson, Esq., Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ, 08933-7003
NUMBER OF CLAIMS:	27
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	6 Drawing Page(s)
LINE COUNT:	2046

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0071] Nucleotide sequences that are complementary to the protease T encoding DNA sequence can be synthesized for **antisense** therapy. These **antisense** molecules may be DNA, stable derivatives of DNA such as phosphorothioates or methylphosphonates, RNA, stable derivatives of RNA such as 2'-O-alkylRNA, or other protease T **antisense** oligonucleotide mimetics. protease T **antisense** molecules may be introduced into cells by microinjection, liposome encapsulation or by expression from vectors harboring the **antisense** sequence. protease T **antisense** therapy may be particularly useful for the treatment of diseases where it is beneficial to reduce protease T expression or. . .

DETD . . . is highly restricted to specific tissues and cell types. The tissue types found to express the protease T transcript are **placenta**, stomach, testis, retina, fibroblasts, spinal cord, and several regions of the brain. Protease T mRNA is also found in leukocytes. . .

DETD [0166] Ishii, K., Hein, L., Kobilka, B., and Coughlin, S. R. (1993). Kinetics of **thrombin receptor** cleavage on intact cells. Relation to signaling. J. Biol. Chem. 268, 9780-6.

L14 ANSWER 5 OF 70 USPATFULL

ACCESSION NUMBER:	2002:294724 USPATFULL
TITLE:	DNA encoding the human serine protease C-E
INVENTOR(S):	Darrow, Andrew, Lansdale, PA, UNITED STATES Qi, Jenson, Branchburg, NJ, UNITED STATES Andrade-Grodon, Patricia, Doylestown, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002164767	A1	20021107
APPLICATION INFO.:	US 2002-40803	A1	20020107 (10)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1999-386629, filed on 31 Aug 1999, PENDING
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Philip S. Johnson, Esq., Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ, 08933-7003
NUMBER OF CLAIMS:	27
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	5 Drawing Page(s)
LINE COUNT:	2065

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . a member of the S1 serine protease family. We have found that

the protease C-E mRNA is expressed in pancreas, **placenta**, prostate, small intestine, stomach, spleen, fibroblasts and epidermis, as well as in certain regions of the brain i.e., cerebellum, cerebral. . .

DETD . . . types will contain the described protease. Vertebrate cells capable of producing protease C-E include, but are not limited to pancreas, **placenta**, prostate, small intestine, stomach and spleen. Other tissue types may be human cerebellum, cerebral cortex, pituitary and hippocampus as well. . .

DETD [0069] Protease C-E is expressed in pancreas, **placenta**, prostate, small intestine, stomach and spleen where it may perform roles in normal physiology or during various pathological states. Other. . .

DETD [0073] Nucleotide sequences that are complementary to the protease C-E encoding DNA sequence can be synthesized for **antisense** therapy. These **antisense** molecules may be DNA, stable derivatives of DNA such as phosphorothioates or methylphosphonates, RNA, stable derivatives of RNA such as 2'-O-alkylRNA, or other protease C-E **antisense** oligonucleotide mimetics. protease C-E **antisense** molecules may be introduced into cells by microinjection, liposome encapsulation or by expression from vectors harboring the **antisense** sequence, protease C-E **antisense** therapy may be particularly useful for the treatment of diseases where it is beneficial to reduce protease C-E expression or. . .

DETD . . . mRNA is highly restricted to specific tissues and cell types. The tissue types expressing the protease C-E transcript are pancreas, **placenta**, prostate, small intestine, stomach, spleen, fibroblasts and epidermis, as well as in certain regions of the brain i.e., cerebellum, cerebral. . .

DETD [0170] Ishii, K., Hein, L., Kobilka, B., and Coughlin, S. R. (1993). Kinetics of **thrombin receptor** cleavage on intact cells. Relation to signaling. J. Biol. Chem. 268, 9780-6.

L14 ANSWER 6 OF 70 USPATFULL

ACCESSION NUMBER:	2002:294294 USPATFULL
TITLE:	Bifunctional molecules and vectors complexed therewith for targeted gene delivery
INVENTOR(S):	Nemerow, Glen R., Encinitas, CA, UNITED STATES Li, Erguang, San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S):	The Scripps Research Institute (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002164333	A1	20021107	
APPLICATION INFO.:	US 2001-903327	A1	20010710	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-325781P	20000710 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	STEPHANIE SEIDMAN, HELLER EHRMAN WHITE & MCAULIFFE LLP, 4350 LA JOLLA VILLAGE DRIVE, 7th FL., SAN DIEGO, CA, 92122-1246
NUMBER OF CLAIMS:	39
EXEMPLARY CLAIM:	1
LINE COUNT:	3999

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . an II-4 receptor, an IgM receptor, a CD4 receptor, a CD2 receptor, a CD3/T cell receptor, a G protein linked **thrombin receptor**, an ATP receptor, an fMLP receptor, and tyrosine kinase receptors that, when activated, result in increased accumulation of Ptdins(3, 4,. . .

SUMM [0077] Therefore, therapeutic nucleotide nucleic acid molecules include **antisense** sequences or nucleotide sequences which may be

transcribed into **antisense** sequences. Therapeutic nucleotide sequences (or transgenes) all include nucleic acid molecules that function to produce a desired effect in the. . .

SUMM . . . CD2 receptor, and the CD3/T cell receptor. Other receptors, such as the cytokine II-4 receptor and the G protein linked **thrombin receptor**, ATP receptor, and the fMLP receptor, that stimulate the activity of a PI3K, resulting in subsequent Ptdlns(3, 4, 5)P3 accumulation. . .

SUMM [0235] The recombinant viral compositions may also be formulated for **implantation** into tissues, including as the anterior or posterior chamber of the eye, particularly the vitreous cavity, in sustained released formulations,. . .

DETD . . . GCC ACC ATG GGA TGG AGC TGG ATC T (SEQ ID. NO. 21) having a KpnI restriction site, and the "**antisense**" primer 5'-GAA TTC ATG TAA CAC AGA GCA GGA (SEQ ID. NO. 22) having an EcoRI restriction site, for PCR. . . ACC ATG GAG ACA GAC ACA ATC CTG CT (SEQ ID. NO. 23) having a HindIII restriction site, and the "**antisense**" primer 5'-TCT AGA TGT CTC TAA CAC TCA TTC CTG T (SEQ ID. NO. 24) having an Xbal restriction site,. . .

DETD . . . vector using the "sense" primer sequence set forth in SEQ ID. NO. 21 (having a Kpnl restriction site), and the "**antisense**" primer 5'-GAA TTC TGA TAC TTC TGG GAC TGT (SEQ ID. NO. 25 with an an EcoRI restriction site).

DETD . . . For amplification of TNF-.alpha., "sense" primer 5'-GAA TTC GTC AGA TCA TCT TCT CGA AC (SEQ ID. NO. 26) and "**antisense**" primer 5'-GAA TTC TAC AGG GCA ATG ATC CCA AA (SEQ ID. NO. 27); for amplification of IGF-1, "sense" primer 5'-GAA TTC GGA CCG GAG ACG CTC TGC GG (SEQ ID. NO. 28) and "**antisense**" primer 5'-GAA TTC TAA GCT GAC TTG GCA GGC TT (SEQ ID. NO. 29); for amplification of EGF, "sense" primer. . . CAT GAT GGT GTG TGC ATG TAT ATT GAA GCA TTG GAC AAG TAT GCA (SEQ ID. NO. 30) and "**antisense**" primer 5'-GAA TTC TAG CGC AGT TCC CAC CAC TTC AGG TCT CGG TAC TGA CAT CGC TCC CCG ATG. . .

DETD . . . using the following primers: "sense" primer 5'-GCG GCC GCA AGG GAT CTG CAG GAA TCG (SEQ ID. NO. 32) and "**antisense**" primer 5'-TCT AGA GTG CAA CAG GGG GTA ACA TA (SEQ ID. NO. 33). Generation of the Noti site at. . .

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 22
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: PCR **antisense** primer for subcloning DAV-1 heavy chain for whole antibody construct.
SEQUENCE: 22
gaattcatgt aacacagagc agga 24

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 24
LENGTH: 28
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: PCR **antisense** primer for subcloning DAV-1 light chain for whole antibody or Fab+402 constructs.
SEQUENCE: 24
tctagatgtc tctaacactc attcctgt 28

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 25
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: PCR **antisense** primer for subcloning DAV-1 heavy chain for Fab'2 constructs.

SEQUENCE: 25
gaattctgat acttctggga ctgt 24
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 27
LENGTH: 26
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: PCR **antisense** primer for subcloning TNF. into DAV-1/TNF. fusion construct.
SEQUENCE: 27
gaattctaca gggcaatgat cccaaa 26
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 29
LENGTH: 26
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: PCR **antisense** primer for subcloning IGF-1 into DAV-1/IGF-1 fusion construct.
SEQUENCE: 29
gaattctaag ctgacttggc aggctt 26
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 31
LENGTH: 98
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: PCR **antisense** primer for subcloning EGF into DAV-1/EGF fusion construct.
SEQUENCE: 31
gaattctagc gcagttccca ccacttcagg tctcggtact gacatcgctc cccgatgtag 60
ccaacaacac agttgcatgc atacttgtcc aatgcttc. . .
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 33
LENGTH: 26
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: PCR **antisense** primer for subcloning SCF into DAV-1/SCF fusion construct.
SEQUENCE: 33
tctagagtgc aacaggggt aacata 26
CLM What is claimed is:
. . . an II-4 receptor, an IgM receptor, a CD4 receptor, a CD2 receptor, a CD3/T cell receptor, a G protein linked **thrombin receptor**, an ATP receptor, and an fMLP receptor.

L14 ANSWER 7 OF 70 USPATFULL
ACCESSION NUMBER: 2002:280092 USPATFULL
TITLE: Regulation of human CysLT2-like GPCR protein
INVENTOR(S): Xiao, Yonghong, Cambridge, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002155528	A1	20021024	
APPLICATION INFO.:	US 2001-828478	A1	20010409	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-195196P	20000407	(60)
	US 2000-254876P	20001213	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100, WASHINGTON, DC, 20001
NUMBER OF CLAIMS: 61
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 19 Drawing Page(s)
LINE COUNT: 3518
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . of SEQ ID NO: 1 or its complement. Such polynucleotides can be used, for example, as hybridization probes or as **antisense** oligonucleotides.

DETD [0131] **Antisense** Oligonucleotides

DETD [0132] **Antisense** oligonucleotides are nucleotide sequences which are complementary to a specific DNA or RNA sequence. Once introduced into a cell, the. . . nucleotides combine with natural sequences produced by the cell to form complexes and block either transcription or translation. Preferably, an **antisense** oligonucleotide is at least 11 nucleotides in length, but can be at least 12, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides long. Longer sequences also can be used. **Antisense** oligonucleotide molecules can be provided in a DNA construct and introduced into a cell as described above to decrease the. . .

DETD [0133] **Antisense** oligonucleotides can be deoxyribonucleotides, ribonucleotides, or a combination of both. Oligonucleotides can be synthesized manually or by an automated synthesizer,. . .

DETD [0134] Modifications of CysLT2-like GPCR protein gene expression can be obtained by designing **antisense** oligonucleotides which will form duplexes to the control, 5', or regulatory regions of the CysLT2-like GPCR protein gene. Oligonucleotides derived. . . ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or chaperons. Therapeutic advances using **triplex** DNA have been described in the literature (e.g., Gee et al., in Huber & Carr, MOLECULAR AND IMMUNOLOGIC APPROACHES, Futura Publishing Co., Mt. Kisco, N.Y., 1994). An **antisense** oligonucleotide also can be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

DETD [0135] Precise complementarity is not required for successful complex formation between an **antisense** oligonucleotide and the complementary sequence of a CysLT2-like GPCR polynucleotide. **Antisense** oligonucleotides which comprise, for example, 2, 3, 4, or 5 or more stretches of contiguous nucleotides which are precisely complementary. . . 3, or 4 nucleotides in length. One skilled in the art can easily use the calculated melting point of an **antisense** -sense pair to determine the degree of mismatching which will be tolerated between a particular **antisense** oligonucleotide and a particular CysLT2-like GPCR polynucleotide sequence.

DETD [0136] **Antisense** oligonucleotides can be modified without affecting their ability to hybridize to a CysLT2-like GPCR polynucleotide. These modifications can be internal or at one or both ends of the **antisense** molecule. For example, internucleoside phosphate linkages can be modified by adding cholesteryl or diamine moieties with varying numbers of carbon. . . in which the 3' hydroxyl group or the 5' phosphate group are substituted, also can be employed in a modified **antisense** oligonucleotide. These modified oligonucleotides can be prepared by methods well known in the art. See, e.g., Agrawal et al., Trends. . .

DETD . . . an RNA sequence, as is known in the art (e.g., Haseloff et al., U.S. Pat. No. 5,641,673). The mechanism of **ribozyme** action involves sequence-specific hybridization of the **ribozyme** molecule to complementary target RNA, followed by endonucleolytic cleavage. Examples include engineered hammerhead motif **ribozyme** molecules that can specifically and efficiently catalyze endonucleolytic cleavage of specific nucleotide sequences.

DETD . . . example, the cleavage activity of ribozymes can be targeted to specific RNAs by engineering a discrete "hybridization" region into the **ribozyme**. The hybridization region contains a sequence

complementary to the target RNA and thus specifically hybridizes with the target (see, for. . .

DETD [0140] Specific **ribozyme** cleavage sites within a CysLT2-like GPCR protein RNA target can be identified by scanning the target molecule for **ribozyme** cleavage sites which include the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and. . . be used to increase the affinity of the hybridization sequence for the target. The hybridizing and cleavage regions of the **ribozyme** can be integrally related such that upon hybridizing to the target RNA through the complementary regions, the catalytic region of the **ribozyme** can cleave the target.

DETD . . . DNA construct. Mechanical methods, such as microinjection, liposome-mediated transfection, electroporation, or calcium phosphate precipitation, can be used to introduce a **ribozyme**-containing DNA construct into cells in which it is desired to decrease CysLT2-like GPCR protein expression. Alternatively, if it is desired. . . maintained as a separate element or integrated into the genome of the cells, as is known in the art. A **ribozyme**-encoding DNA construct can include transcriptional regulatory elements, such as a promoter element, an enhancer or UAS element, and a transcriptional. . .

DETD [0142] As taught in Haseloff et al., U.S. Pat. No. 5,641,673, ribozymes can be engineered so that **ribozyme** expression will occur in response to factors which induce expression of a target gene. Ribozymes also can be engineered to provide an additional level of regulation, so that destruction of mRNA occurs only when both a **ribozyme** and a target gene are induced in the cells.

DETD . . . described herein in an appropriate animal model. For example, an agent identified as described herein (e.g., a modulating agent, an **antisense** nucleic acid molecule, a specific antibody, **ribozyme**, or a CysLT2-like GPCR polypeptide binding molecule) can be used in an animal model to determine the efficacy, toxicity, or. . .

DETD [0227] Complexing a liposome with a reagent such as an **antisense** oligonucleotide or **ribozyme** can be achieved using methods which are standard in the art (see, for example, U.S. Pat. No. 5,705,151). Preferably, from. . .

DETD [0238] If the expression product is mRNA, the reagent is preferably an **antisense** oligonucleotide or a **ribozyme**. Polynucleotides which express **antisense** oligo-nucleotides or ribozymes can be introduced into cells by a variety of methods, as described above.

DETD [0297] Synthesis of **antisense** CysLT2-like GPCR oligonucleotides comprising at least 11 contiguous nucleotides selected from the complement of SEQ ID NO:1 is performed on. . .

DETD [0298] The **antisense** oligonucleotides are administered intrabronchially to a patient with asthma. The severity of the patient's asthma is lessened.

DETD . . . expression is detected in the fetal and adult brain compared to high expression in heart, lung, colon, small intestine and **placenta**. Even low expression in the CNS, specific expression of the CysLT2-like GPCR indicates the possibility to treat various disorders of. . .

DETD . . . IV, K4003-1

20. fetal liver	Clontech	Human Total RNA Panel IV, K4003-1
21. spinal cord	Clontech	Human Total RNA Panel IV, K4003-1
22. **placenta**	Clontech	Human Total RNA Panel IV, K4003-1
23. adrenal gland	Clontech	Human Total RNA Panel V. K4004-1
24. pancreas	Clontech	Human Total RNA. . .

DETD . . . on average in the tissues tested (roughly one-tenth the amount per cell) and shows relatively more pronounced expression in the **placenta**.

DETD . . . Liver OriGene (MD) HT1005
h. Thymus Clontech (CA) 640281

	h. Testis	OriGene (MD) HT1011
	h. Colon	OriGene (MD) HT1015
	h. **Placenta**	OriGene (MD) HT1013
	h. Trachea	Clontech 640911
	h. Pancreas	Clontech 640311
	h. Gastric Mucosa	From autopsy
	h. Fetal Liver	Clontech. . .

DETD [0361] Leukotriene D4 (LTD4) and Protease activated receptor-1 (**PAR-1**) activating peptide (H-Ser-Phe-Lue-Lue-Arg-Asn-NH.sub.2, SEQ ID NO:16) were purchased from Sigma and Bachem, respectively. The results obtained are shown FIGS. 12,. . .

DETD . . . antagonists were evaluated against 2 nM and 0.2 nM LTD4 for CysLT2R and CysLT1R transfected cells, respectively. Protease activated receptor-1 (**PAR-1**) is an endogenous Gq-coupled receptor in PEAK-stable cells. Ten .mu.M of **PAR-1** activating peptide was used to stimulate the receptor on the cells stably transfected with vacant vector. The selected concentration of. . .

CLM What is claimed is:

42. The method of claim 41 wherein the reagent is an **antisense** oligonucleotide.

43. The method of claim 41 wherein the reagent is a **ribozyme**.

49. The pharmaceutical composition of claim 48 wherein the reagent is a **ribozyme**.

50. The pharmaceutical composition of claim 48 wherein the reagent is an **antisense** oligonucleotide.

L14 ANSWER 8 OF 70 USPATFULL

ACCESSION NUMBER:	2002:265929 USPATFULL
TITLE:	DNA encoding the human serine protease T
INVENTOR(S):	Darrow, Andrew, Lansdale, PA, UNITED STATES Qi, Jenson, Branchburg, NJ, UNITED STATES Andrade-Grodon, Patricia, Doylestown, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002146805	A1	20021010
APPLICATION INFO.:	US 2002-40655	A1	20020107 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-386653, filed on 31 Aug 1999, PENDING

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Philip S. Johnson, Esq., Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ, 08933-7003
NUMBER OF CLAIMS:	27
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	6 Drawing Page(s)
LINE COUNT:	2049

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0072] Nucleotide sequences that are complementary to the protease T encoding DNA sequence can be synthesized for **antisense** therapy. These **antisense** molecules may be DNA, stable derivatives of DNA such as phosphorothioates or methylphosphonates, RNA, stable derivatives of RNA such as 2'-O-alkyll RNA, or other protease T **antisense** oligonucleotide mimetics. protease T **antisense** molecules may be introduced into cells by microinjection, liposome encapsulation or by expression from vectors harboring the **antisense** sequence. protease T **antisense** therapy may be particularly useful for the treatment of diseases where it is beneficial to reduce protease T expression or. . .

DETD . . . is highly restricted to specific tissues and cell types. The

tissue types found to express the protease T transcript are **placenta**, stomach, testis, retina, fibroblasts, spinal cord, and several regions of the brain. Protease T mRNA is also found in leukocytes. . .

DETD [0168] Ishii, K., Hein, L., Kobilka, B., and Coughlin, S. R. (1993). Kinetics of **thrombin receptor** cleavage on intact cells. Relation to signaling. J. Biol. Chem. 268, 9780-6.

L14 ANSWER 9 OF 70 USPATFULL

ACCESSION NUMBER: 2002:258714 USPATFULL
TITLE: Methods of identifying renal protective factors
INVENTOR(S): Raha, Debasish, New Haven, CT, UNITED STATES
Green, Cyndi D., Madison, CT, UNITED STATES
Cate, Richard L., Weston, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002142284	A1	20021003	
APPLICATION INFO.:	US 2001-905325	A1	20010713	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-217932P	20000713 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MINTZ, LEVIN, COHN, FERRIS,, GLOVSKY AND POPEO, P.C., One Financial Center, Boston, MA, 02111
NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1
LINE COUNT: 2754
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . 1.6 -- 1.6
TIMP-2 mRNA for tissue inhibitor of metalloproteinases.
ABP1 OR DAO1 OR gbem_aa023491 19 9.2 7.4
2.8 -- 2.1 -3.2
AOC1: mh74e11.r1 Soares mouse **placenta** 4NbMP13.5 14.5 Mus musculus cDNA; mouse homolog of diamine oxidase, aka amiloride binding protein, histaminase
CAL1H or ANX2: Mouse gbem_aa689813 20 2.4 3.8
1.9 -1.8 -1.1 6.3
calpactin. . . Mus musculus 102914 54 -1.6
-1.7 -- 1.7 3 -3.3
aquaporin-CHIP (aka water channel protein for red blood cells and kidney proximal tubule, early response protein DER2)
F2R or PAR1 or CF2R: 103529 55 --
2.2 2.3 -- -- 3.8
Mus musculus **thrombin receptor**
FN1: Mouse fibronectin m18194 56 4.9 4.2
1.8 -- -- 2.9
GLUT1 or SLC2A1: m22998 57 1.8 2.1
2.2 -- -- 2.2
Mouse. . .

DETD [0117] **Antisense**

DETD [0118] Another aspect of the invention pertains to isolated **antisense** nucleic acid molecules that are hybridizable to or complementary to the nucleic acid molecule comprising the nucleotide sequence of a RPF sequence or fragments, analogs or derivatives thereof. An "**antisense**" nucleic acid comprises a nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein, e.g., complementary to the coding strand of a double-stranded cDNA molecule or complementary to an MRNA sequence. In specific aspects, **antisense** nucleic acid molecules are provided that comprise a sequence complementary to at least about 10, 25, 50, 100, 250 or. . . or to only a portion thereof. Nucleic acid molecules encoding fragments, homologs, derivatives and analogs of a RPF protein, or **antisense** nucleic acids complementary to a nucleic acid comprising a RPF nucleic acid sequence are additionally provided.

DETD [0119] In one embodiment, an **antisense** nucleic acid molecule is **antisense** to a "coding region" of the coding strand of a nucleotide sequence encoding RPF. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the **antisense** nucleic acid molecule is **antisense** to a "noncoding region" of the coding strand of a nucleotide sequence encoding RPF. The term "noncoding region" refers to. . .

DETD [0120] Given the coding strand sequences encoding RPF disclosed herein, **antisense** nucleic acids of the invention can be designed according to the rules of Watson and Crick or Hoogsteen base pairing. The **antisense** nucleic acid molecule can be complementary to the entire coding region of RPF mRNA, but more preferably is an oligonucleotide that is **antisense** to only a portion of the coding or noncoding region of RPF MRNA. For example, the **antisense** oligonucleotide can be complementary to the region surrounding the translation start site of RPF mRNA. An **antisense** oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An **antisense** nucleic acid of the invention can be constructed using chemical synthesis or enzymatic ligation reactions using procedures known in the art. For example, an **antisense** nucleic acid (e.g., an **antisense** oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the **antisense** and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used.

DETD [0121] Examples of modified nucleotides that can be used to generate the **antisense** nucleic acid include: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxyrnethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine,. . . queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the **antisense** nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an **antisense** orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an **antisense** orientation to a target nucleic acid of interest, described further in the following subsection).

DETD [0122] The **antisense** nucleic acid molecules of the invention are typically administered to a subject or generated in situ such that they hybridize. . . hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an **antisense** nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of **antisense** nucleic

acid molecules of the invention includes direct injection at a tissue site. Alternatively, **antisense** nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, **antisense** molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, e.g., by linking the **antisense** nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens. The **antisense** nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of **antisense** molecules, vector constructs in which the **antisense** nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

DETD [0123] In yet another embodiment, the **antisense** nucleic acid molecule of the invention is an .alpha.-anomeric nucleic acid molecule. An .alpha.-anomeric nucleic acid molecule forms specific double-stranded. . . the usual .beta.-units, the strands run parallel to each other (Gaultier et al. (1987) Nucleic Acids Res 15: 6625-6641). The **antisense** nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue et al. (1987) Nucleic Acids Res 15: 6131-6148) or a chimeric. . .

DETD [0125] In still another embodiment, an **antisense** nucleic acid of the invention is a **ribozyme**. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as an. . . (1988) Nature 334:585-591)) can be used to catalytically cleave RPF mRNA transcripts to thereby inhibit translation of RPF mRNA. A **ribozyme** having specificity for a RPF-encoding nucleic acid can be designed based upon the nucleotide sequence of a RPF DNA disclosed. . .

DETD [0128] PNAs of RPF can be used in therapeutic and diagnostic applications. For example, PNAs can be used as **antisense** or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication. PNAs. . .

DETD . . . about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA that can include sense/**antisense** pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with SI nuclease, and ligating the. . .

DETD . . . further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an **antisense** orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner that allows for expression (by transcription of the DNA molecule) of an RNA molecule that is **antisense** to RPF mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the **antisense** orientation can be chosen that direct the continuous expression of the **antisense** RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen that direct constitutive, tissue specific or cell type specific expression of **antisense** RNA. The **antisense** expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which **antisense** nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined. . . by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using **antisense** genes see Weintraub et al., "**Antisense** RNA as a molecular tool for genetic analysis," Reviews--Trends in Genetics, Vol. 1(1) 1986.

L14 ANSWER 10 OF 70 USPATFULL
ACCESSION NUMBER: 2002:243784 USPATFULL
TITLE: VEGF-modulated genes and methods employing them
INVENTOR(S): Gerber, Hans-Peter, San Francisco, CA, UNITED STATES
Rastelli, Luca, Guilford, CT, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002132978	A1	20020919	
APPLICATION INFO.:	US 2001-815153	A1	20010321	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-191201P	20000322 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BRINKS HOFER GILSON & LIONE, P.O. Box 10395, Chicago, IL, 60610
NUMBER OF CLAIMS: 61
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 5514
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . important therapeutic targets. Over expression of DSCR1 was able to hasten apoptosis in human umbilical vascular endothelial cells (HUVECs), while **antisense** DSCR1 expression promoted cell survival to similar levels as that of activated AKT expression (see FIG. 1).

DETD . . . a multifunctional serine protease that is produced at sites of tissue injury. Thrombin acts via a cell surface protease-activated receptor (**PAR-1**) and increases in intracellular free calcium levels ([Ca2+]i) (Smith-Swintosky et al., 1995). The present invention demonstrates that serine protease inhibitors. . .

DETD . . . in adult and tumor non-vascular tissues. Over-expression of DSCR1 correlates with clinical stage of ovarian cancer. Elimination of DSCR1 by **antisense** experiments increases endothelial cell survival.

DETD [0221] Using **antisense** and sense VEGFmg oligonucleotides can prevent VEGFmg polypeptide expression These oligonucleotides bind to target nucleic acid sequences, forming duplexes that. . .

DETD [0222] **Antisense** or sense oligonucleotides are singe-stranded nucleic acids, either RNA or DNA, which can bind target VEGFmg mRNA (sense) or VEGFmg DNA (**antisense**) sequences. According to the present invention, **antisense** or sense oligonucleotides comprise a fragment of the VEGFmg DNA coding region of at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. In general, **antisense** RNA or DNA molecules can comprise at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60,. . . in length or more. Among others, (Stein and Cohen, 1988; van der Krol et al., 1988a) describe methods to derive **antisense** or a sense oligonucleotides from a given cDNA sequence.

DETD [0223] Modifications of **antisense** and sense oligonucleotides can augment their effectiveness. Modified sugar-phosphodiester bonds or other sugar linkages (WO 91/06629, 1991), increase in vivo. . .

DETD [0224] To introduce **antisense** or sense oligonucleotides into target cells (cells containing the target nucleic acid sequence), any gene transfer method may be used. . .

DETD . . . Molecules that can act as agonists or antagonists include Abs or antibody fragments, fragments or variants of endogenous VEGFmg, peptides, **antisense** oligonucleotides, small organic molecules, etc.

DETD . . . (1) small organic and inorganic compounds, (2) small peptides, (3) Abs and derivatives, (4) polypeptides closely related to VEGFmg, (5) **antisense** DNA and RNA, (6) ribozymes, (7) triple DNA helices and (8) nucleic acid aptamers.

DETD [0302] **Antisense** RNA or DNA constructs can be effective antagonists. **Antisense** RNA or DNA molecules block function by inhibiting translation by hybridizing to targeted mRNA **Antisense** technology can be used to control gene expression through triple-helix formation or **antisense** DNA or RNA, both of which depend on

polynucleotide binding to DNA or RNk For example, the 5' coding portion of the VEGFmg sequence is used to design an **antisense** RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary. . . and Dervan, 1991; Cooney et al., 1988; Lee et al., 1979), preventing transcription and the production of the VEGFmg. The **antisense** RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into the VEGFmg (**antisense**) (Cohen, 1989; Okano et al., 1991). These oligonucleotides can also be delivered to cells such that the **antisense** RNA or DNA may be expressed in vivo to inhibit production of the VEGFmg. When **antisense** DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene. . .

DETD . . . the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific **ribozyme** cleavage sites within a potential RNA target can be identified by known techniques (WO 97/33551, 1997; Rossi, 1994).

DETD . . . sequence specific ribozymes can be used to score for the presence of specific mutations by development or loss of a **ribozyme** cleavage site.

DETD . . . or analogs, derivatives, fragments or homologs thereof; (2) Abs to a VEGFmg peptide; (3) VEGFmg nucleic acids; (4) administration of **antisense** nucleic acid and nucleic acids that are "dysfunctional" (i.e., due to a heterologous insertion within the coding sequences) that are. . .

DETD . . . that has been introduced into the cell. In another embodiment, the agent inhibits VEGFmg activity. Examples of inhibitory agents include **antisense** VEGFmg nucleic acids and anti-VEGFmg Abs. Modulatory methods can be performed in vitro (e.g., by culturing the cell with the. . .

DETD [0416] Using **antisense** and sense VEGFmg oligonucleotides can prevent VEGFmg polypeptide expression These oligonucleotides bind to target nucleic acid sequences, forming duplexes that. . .

DETD [0417] **Antisense** or sense oligonucleotides are singe-stranded nucleic acids, either RNA or DNA, which can bind target VEGFmg mRNA (sense) or VEGFmg DNA (**antisense**) sequences. Anti-sense nucleic acids can be designed according to Watson and Crick or Hoogsteen base pairing rules. The anti-sense nucleic. . . mRNA For example, the anti-sense oligonucleotide can be complementary to the region surrounding the translation start site of VEGFmg mRNA. **Antisense** or sense oligonucleotides may comprise a fragment of the VEGFmg DNA coding region of at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. In general, **antisense** RNA or DNA molecules can comprise at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60,. . . in length or more. Among others, (Stein and Cohen, 1988; van der Krol et al., 1988a) describe methods to derive **antisense** or a sense oligonucleotides from a given cDNA sequence.

DETD [0419] To introduce **antisense** or sense oligonucleotides into target cells (cells containing the target nucleic acid sequence), any gene transfer method may be used.. . .

DETD [0420] An **antisense** or sense oligonucleotide is inserted into a suitable gene transfer retroviral vector. A cell containing the target nucleic acid sequence. . .

DETD . . . cells in a mixed population of cells cell surface receptors that are specific to the target cells can be exploited. **Antisense** and sense oligonucleotides are conjugated to a ligand-binding molecule, as described in (WO 91/04753, 1991). Ligands are chosen for receptors. . . the ability of the receptors or molecule to bind the ligand-binding molecule conjugate, or block entry of the sense or **antisense** oligonucleotide or its conjugated version into the cell.

DETD [0422] Liposomes efficiently transfer sense or an **antisense** oligonucleotide to cells (WO 90/10448, 1990). The sense or

antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

DETD [0424] In one embodiment, an anti-sense nucleic acid of the invention is a **ribozyme**. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as an. . . hammerhead ribozymes (Haseloff and Gerlach, 1988) can be used to catalytically cleave VEGFmg mRNA transcripts and thus inhibit translation A **ribozyme** specific for a VEGFmg-encoding nucleic acid can be designed based on the nucleotide sequence of a VEGFmg cDNA. For example,. . .

DETD [0426] Modifications of **antisense** and sense oligonucleotides can augment their effectiveness. Modified sugar-phosphodiester bonds or other sugar linkages (WO 91/06629, 1991), increase in vivo. . .

DETD [0440] **Placenta** growth factor (PIGF) belongs to the family of VEGFs (VEGFs). Three PlGF isoforms are produced by alternative splicing and all. . .

DETD [0451] Formalin fixed, paraffin-embedded human tissues were investigated for in situ mRNA expression. Tissues included first trimester (14-15 week) **placenta**, adult adrenal cortex, aorta, muscular artery with atherosclerosis, brain, gall bladder, heart, pancreas, prostate, stomach, eye with age related macular. . . analyzed were PCR-amplified from plasmid DNA using gene-specific primers that encoded T3 or T7 RNA polymerase initiation sites. Sense and **antisense** riboprobes were prepared by in vitro transcription from the PCR -amplified templates and diluted in hybridization buffer to a specific. . .

DETD . . . transient overexpression of epitope tagged version of DSCR1 (DSCR1-FLAG) led to a modest decrease in cell viability. Overexpression of the **antisense** construct, in contrast, increased survival to similar extends as observed for a constitutive active form of Akt (Akt 179). These. . .

DETD [0460] Expression in HUVECs of sense and **antisense** polynucleotides corresponding to genes in this invention was carried out as follows:

DETD [0579] WO 91/04753. Conjugates of **antisense** oligonucleotides and therapeutic uses thereof 1991.

DETD [0599] Athanassiades, A., and P. K. Lala. 1998. Role of **placenta** growth factor (PIGF) in human extravillous trophoblast proliferation, migration and invasiveness. **Placenta**. 19:465-73.

DETD [0627] U.S. Pat. No. 5,116,742. RNA **ribozyme** restriction endoribonucleases and methods. 1992.

DETD [0628] U.S. Pat. No. 4,987,071. RNA **ribozyme** polymerases, dephosphorylases, restriction endoribonucleases and methods. 1991.

DETD [0635] Cohen, A. S., D. L. Smisek, and B. H. Wang. 1996. Emerging technologies for sequencing **antisense** oligonucleotides: capillary electrophoresis and mass spectrometry. Adv Chromatogr. 36:127-62.

DETD [0636] Cohen, J. S. 1989. Oligodeoxynucleotides: **Antisense** inhibitors of gene expression. CRC Press, Boca Raton, Fla. 255 pp.

DETD [0701] Helene, C. 1991. The anti-gene strategy: control of gene expression by **triplex**-forming- oligonucleotides. Anticancer Drug Des. 6:569-84.

DETD [0713] Inaba, N., H. Ishige, M. Ijichi, N. Satoh, et al. 1982. Immunohistochemical detection of pregnancy-specific protein (SP1) and **placenta**-specific tissue proteins (PP5, PP10, PP11 and PP12) in ovarian adenocarcinomas. Oncodev Biol Med. 3:379-89.

DETD [0775] Migdal, M., B. Huppertz, S. Tessler, A. Comforti et al. 1998. Neuropilin-1 is a **placenta** growth factor-2 receptor. J Biol Chem. 273:22272-8.

DETD [0795] Okano, H., J. Aruga, T. Nakagawa, C. Shiota, et al. 1991. Myelin basic protein gene and the function of **antisense** RNA in its repression in myelin-deficient mutant mouse. J Neurochem. 56:560-7.

L14 ANSWER 11 OF 70 USPATFULL
ACCESSION NUMBER: 2002:235513 USPATFULL

TITLE: Methods and compositions for regulating cell cycle progression

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Coughlin, Shaun R., Tiburon, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002127702	A1	20020912
APPLICATION INFO.:	US 2001-757049	A1	20010108 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-156316, filed on 18 Sep 1998, GRANTED, Pat. No. US 6183961

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PRIORITY INFORMATION:	US 1997-60688P	19970922 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: COOLEY GODWARD LLP, Attention: Patent Group, Five Palo Alto Square, 3000 El Camino Real, Palo Alto, CA, 94306-2155
NUMBER OF CLAIMS: 65
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 21 Drawing Page(s)
LINE COUNT: 3521
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Method and compositions for regulating cell cycle progression are disclosed. Compositions include nucleic acids comprising a human Cdc5 gene, **antisense** gene and fragments thereof and a human Cdc5 protein and polypeptide fragments thereof polypeptide. The consensus DNA binding site for. . .

SUMM [0010] A further aspect of the invention is an **antisense** nucleic acid comprising a nucleic acid sequence complementary to the nucleic acid sequence of FIG. 2D (SEQ ID NO:11).

DETD [0067] In some embodiments, **antisense** antagonists of hCdc5 expression are provided. For a review of the design considerations and use of **antisense** oligonucleotides, see Uhlmann et al. Chemical Reviews 90:543-584 (1990) the disclosure of which is hereby incorporated by reference. The **antisense** oligonucleotides of the present invention may be synthesized by any of the known chemical oligonucleotide synthesis methods. Such methods are. . . described, for example, in Winnacker From Genes to Clones: Introduction to Gene Technology, VCH Verlagsgesellschaft mhH (H. Ibelgaufts trans. 1987). **Antisense** oligonucleotides are advantageously prepared by utilizing any of the commercially available, automated nucleic acid synthesizers. One such device, the Applied. . .

DETD [0068] **Antisense** oligonucleotides hybridizable with any portion of a hCdc5 gene may be prepared by oligonucleotide synthesis methods known to those skilled. . .

DETD . . . specifically bind to hCdc5; antibodies which specifically bind to an hCdc5 co-activator, accessory protein, or target; mutants of hCdc5 protein; **antisense** hCdc5 nucleic acids; co-activators or accessory proteins for hCdc5; and peptide, non-peptide, and peptidomimetic analogs of such co-activators, accessory proteins,. . .

DETD . . . by R. Derynck, University of California San Francisco) with cytoplasmic domains (amino acids 775-799, 1094-1115, and 1274-1512) of the human **thrombin receptor** (Vu, T. et al., Cell 64:1057-1068 (1991)) in the GAL4 binding domain vector, pAS1-CYH (Durfee, T. et al., Genes Devel.. . .

DETD . . . revealed a dominant band at 3.4 kb in all human tissues examined (FIG. 3). In skeletal muscle, heart, pancreas, and **placenta**, a less prominent 8-9 kb band was observed. How this larger mRNA species related to the dominant 3.4-kb species remains. .

DETD . . . the DNA binding domain of hCdc5 binds the double-stranded target sequence specifically. Binding did not occur with single-stranded

sense or **antisense** oligomer. Titration with increasing amounts of purified, recombinant protein enabled us to calculate an equilibrium dissociation constant of .about.10.sup.-8 molar.. . .

CLM What is claimed is:

22. The method of claim 15, wherein the antagonist is an hCdc5 **antisense** nucleic acid.

34. The method of claim 26, wherein the antagonist is an hCdc5 **antisense** nucleic acid.

L14 ANSWER 12 OF 70 USPATFULL

ACCESSION NUMBER: 2002:213791 USPATFULL

TITLE: Isolation of drosophila and human polynucleotides encoding **PAR-1** kinase, polypeptides encoded by the polynucleotides and methods utilizing the polynucleotides and polypeptides

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PATENT INFORMATION:	US 2002115167	A1	20020822	
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PRIORITY INFORMATION:	US 2000-221860P	20000728	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Chiron Corporation, Intellectual Property R338, P.O. Box 8097, Emeryville, CA, 94662-8097
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
LINE COUNT: 11068
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Isolation of drosophila and human polynucleotides encoding **PAR-1** kinase, polypeptides encoded by the polynucleotides and methods utilizing the polynucleotides and polypeptides

AB Isolated nucleic acid molecules comprising polynucleotide having sequences that encode human and Drosophila **PAR-1** kinases. Also provided are proteins and polypeptides encoded by the nucleic acid molecules, methods of modulating **PAR-1** expression and function, and methods of modulating the Wnt signaling pathway.

SUMM . . . products. More specifically, this invention relates to the discovery of a new effector, a Dishevelled associated kinase referred to as **PAR-1**, in Drosophila, and to the discovery and cloning of three structural and functional human homologues of **PAR-1**, referred to as **PAR-1** A, PAR-B (.alpha. and .beta.), and PAR-1C.

SUMM [0007] This invention relates to the discovery of a new effector, a Dishevelled associated kinase referred to as **PAR-1**, in Drosophila, and to the discovery and cloning of three structural and functional human homologues of **PAR-1**, referred to as PAR-1A, PAR-B (.alpha. and .beta.), and PAR-1C, whose mRNA levels increase in response to Wnt. According to the invention, **PAR-1** activates the Wnt pathway and is required for Wnt signaling in mammalian cells.

SUMM [0008] The kinase activity of the **PAR-1** is also stimulated during Wnt signaling. **PAR-1** activates the Wnt pathway through its interaction with Dsh in mammalian cells.

Suppression of endogenous **PAR-1** function inhibits Wnt signaling in mammalian cells and in Xenopus. Importantly, suppression of endogenous **PAR-1** significantly reduces the number of colonies of human colon cancer cells. The data indicate a key role of **PAR-1** as a positive regulator of the Wnt pathway and in the maintenance of a cancer phenotype.

SUMM [0009] Accordingly, the invention relates to novel human kinases that associate with the Dishevelled protein, and are referred to as **PAR-1**.

SUMM [0010] The invention further relates to four human forms of **PAR-1**, referred to as PAR-1A, PAR-1B.alpha., PAR-1B.beta., and **PAR-1** C.

SUMM [0011] The invention still further relates to a Drosophila homolog of **PAR-1**.

SUMM [0012] The invention further relates to polynucleotides encoding **PAR-1**.

SUMM [0013] The invention also relates to variants and homologs of the polynucleotides encoding **PAR-1**.

SUMM [0014] The invention still further relates to proteins sharing the biological function of **PAR-1**, but having at least one amino acid substitution, addition, or deletion relative to corresponding native **PAR-1**.

SUMM [0015] The invention also relates to fragments of **PAR-1**, wherein the fragments retain at least one biological activity of the native protein.

SUMM [0016] The invention further relates to antibodies capable of specifically binding to at least one of the proteins **PAR-1**.

SUMM . . . further relates to a complex comprising a Dishevelled protein or a fragment thereof, and at least one of the proteins **PAR-1**, or a fragment thereof capable of binding to the Dishevelled protein or fragment of the Dishevelled protein.

SUMM [0018] The invention also relates to a method of modulating the Wnt pathway using **PAR-1**.

SUMM . . . invention still further relates to a method of modulating Wnt signaling in a mammalian cell by expressing a variant of **PAR-1**, in the mammalian cell.

SUMM [0020] The invention also relates to agonists and antagonists of these **PAR-1** proteins, knock-outs of the genes, gene therapy, **antisense** and ribozymes that target **PAR-1** mRNA, and blocking antibodies.

SUMM [0034] In a further embodiment, the invention provides a method of identifying an inhibitor or enhancer of **PAR-1** phosphorylation activity. This method comprises contacting a cell transfected with at least an expression vector encoding Wnt with a candidate. . .

SUMM . . . a further embodiment, the invention provides a method of treating a mammal with a disease or disorder associated with a **PAR-1** polypeptide, comprising administering to the mammal a composition including a therapeutically effective amount of a polypeptide having an amino sequence. . .

SUMM . . . still further embodiment, the invention provides a method of treating a mammal with a disease or disorder associated with a **PAR-1** polypeptide, comprising administering to the mammal a composition including a therapeutically effective amount of a polynucleotide having a sequence capable of binding a mammalian **PAR-1** polynucleotide or complement thereof. Preferably, the polynucleotide is an **antisense** oligonucleotide or a **ribozyme** construct. The **antisense** oligonucleotide can be selected, but not limited to, the group consisting of SEQ ID NO:13, SEQ ID NO:15 and SEQ. . .

SUMM [0037] The present also provides, in another embodiment an isolated **PAR-1** modulator selected from the group consisting of an **antisense** oligonucleotide, a **ribozyme**, a protein, a polypeptide, and a small molecule. An example of a **PAR-**

1 modulator is an **antisense** molecule or the complement thereof that comprises at least 15 consecutive nucleic acids of the sequence of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:9 or SEQ ID NO:12. The **antisense** molecule or the complement thereof can also be a sequence that hybridizes under high stringency conditions to the at least. . . nucleic acids of the sequence of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:9 or SEQ ID NO:12. The **antisense** oligonucleotide can also be selected, but not limited to, the group consisting of SEQ ID NO:13, SEQ ID NO:15 and SEQ ID NO:17. Another example of a **PAR** **-1** modulator is an antibody or an antibody fragment. Preferably, the antibody or antibody fragment is a humanized monoclonal. A further example of the **PAR-1** modulator is a polypeptide having an amino sequence with at least 95% identity to the amino acid sequence provided in. . .

SUMM [0038] In another embodiment, the invention provides a composition, comprising a therapeutically effective amount of a **PAR-** **1** modulator as described above in a pharmaceutically acceptable carrier. The composition can comprise two or more **PAR-** **1** modulators.

SUMM [0039] In another embodiment, the invention provides a method of decreasing the expression of **PAR-1** in a mammalian cell, comprising administering to the cell, a PAR-1modulator as described above. The **PAR-1** modulator can be administered ex vivo to the mammalian cell.

SUMM . . . some or all of the same biological properties in a similar fashion, not necessarily to the same degree as the **PAR-** **1** isolated as described herein or recombinantly produced human **PAR-1** of the invention.

SUMM . . . odds value of greater than or equal to 0.3 in the PAM250 residue weight table). Conservation is referenced to human **PAR** **-1** when determining percent conservation with non-human **PAR-1**, and referenced to **PAR-1** when determining percent conservation with non-**PAR-1** Dishevelled-associated proteins. Conservative amino acid changes satisfying this requirement are: R-K; E-D, Y-F, L-M; V-I, Q-H.

SUMM [0045] The invention provides polypeptide fragments of **PAR-** **1**. Polypeptide fragments of the invention can comprise at least 8, 9, 10, 12, 15, 18, 19, 20, 25, 50, 75,. . .

SUMM [0070] Variants of the **PAR-1** protein disclosed herein include glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties. Covalent variants. . .

SUMM [0072] Preferably, amino acid changes in the **PAR-1** protein or polypeptide variants are conservative amino acid changes, ie., substitutions of similarly charged or uncharged amino acids. A conservative. . .

SUMM . . . have a major effect on the biological properties of the resulting secreted protein or polypeptide variant. Properties and functions of **PAR-1** protein or polypeptide variants are of the same type as a protein comprising the amino acid sequence encoded by the. . .

SUMM [0074] **PAR-1** protein variants include glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties. **PAR-1** protein variants also include allelic variants, species variants, and muteins. Truncations or deletions of regions which do not affect the differential expression of the **PAR-1** protein gene are also variants. Covalent variants can be prepared by linking functionalities to groups which are found in the. . .

SUMM [0075] It will be recognized in the art that some amino acid sequence of the **PAR-1** protein of the invention can be varied without significant effect on the structure or function of the protein. If such. . .

SUMM [0076] The invention further includes variations of the **PAR-** **1** polypeptide which show comparable expression patterns or which

include antigenic regions. Such mutants include deletions, insertions, inversions, repeats, and type. . .

SUMM [0081] Fusion proteins comprising proteins or polypeptide fragments of **PAR-1** can also be constructed. Fusion proteins are useful for generating antibodies against amino acid sequences and for use in various. . . art and can also be used as drug screens. Fusion proteins comprising a signal sequence and/or a transmembrane domain of **PAR-1** or a fragment thereof can be used to target other protein domains to cellular locations in which the domains are. . .

SUMM . . . NO:3, 6, 9, 12 or 21, such as those described above. The first protein segment can consist of a full-length **PAR-1**.

SUMM [0086] Isolation and Production of **PAR-1**

SUMM [0087] **PAR-1** is expressed in a variety of human cells and can be extracted from these cells or from other human cells,. . .

SUMM [0089] The resulting expressed **PAR-1** protein can then be purified from the culture medium or from extracts of the cultured cells using purification procedures known. . .

SUMM [0091] **PAR-1** protein or polypeptide of the invention can also be expressed in cultured host cells in a form that will facilitate. . .

SUMM [0095] A gene which encode the **PAR-1** protein of the invention has the coding sequence shown in SEQ ID NO:1 and 2 (hPAR-1A), 4 and 5 (hPAR-1B.alpha.),. . .

SUMM [0112] Degenerate polynucleotide sequences which encode amino acid sequences of the **PAR-1** protein and variants, as well as homologous nucleotide sequences which are at least 65%, 75%, 85%, 90%, 95%, 98%, or. . .

SUMM [0125] **PAR-1** can also include hybrid and modified forms of **PAR-1** including fusion proteins, **PAR-1** fragments and hybrid and modified forms in which certain amino acids have been deleted or replaced, modifications such as where. . . amino acid, and modifications such as glycosylations so long as the hybrid or modified form retains the biological activity of **PAR-1**. By retaining the biological activity of **PAR-1**, it is meant that not necessarily at the same level of potency as that of the **PAR-1** isolated as described herein or that of the recombinantly produced mNkd.

SUMM [0126] Also included within the meaning of substantially homologous is any **PAR-1** which may be isolated by virtue of cross-reactivity with antibodies to the **PAR-1** described herein or whose encoding nucleotide sequences including genomic DNA, mRNA or cDNA may be isolated through hybridization with the complementary sequence of genomic or subgenomic nucleotide sequences or cDNA of the **PAR-1** herein or fragments thereof. It will also be appreciated by one skilled in the art that degenerate DNA sequences can encode **PAR-1** and these are also intended to be included within the present invention as are allelic variants of **PAR-1**.

SUMM [0127] Preferred PAR-1s of the present invention have been identified and isolated in purified forms as described. Also preferred is **PAR-1** prepared by recombinant DNA technology. By "pure form" or "purified form" or "substantially purified form" it is meant that a **PAR-1** composition is substantially free of other proteins which are not **PAR-1**.

SUMM . . . mNkd in an effective amount for treating patients with disease, and a method comprising administering a therapeutically effective amount of **PAR-1**. These compositions and methods are useful for treating a number of diseases including cancer. One skilled in the art can. . .

SUMM [0131] **PAR-1** can also be linked or conjugated with agents that provide desirable pharmaceutical or pharmacodynamic properties. For example, **PAR-1** can be coupled to any substance known in the art to promote penetration or transport across

the blood-brain barrier such. . . and administered by intravenous injection (see, for example, Friden et al., Science 259:373-377, 1993 which is incorporated by reference). Furthermore, **PAR-1** can be stably linked to a polymer such as polyethylene glycol to obtain desirable properties of solubility, stability, half-life and. . .

SUMM . . . for reconstitution by the addition of sterile water for ready injection. The primary solvent can be aqueous or alternatively non-aqueous. **PAR-1** can also be incorporated into a solid or semi-solid biologically compatible matrix which can be implanted into tissues requiring treatment.

SUMM [0135] It is also contemplated that certain formulations containing **PAR-1** are to be administered orally. Such formulations are preferably encapsulated and formulated with suitable carriers in solid dosage forms. Some. . .

SUMM [0137] In one embodiment of this invention, **PAR-1** may be therapeutically administered by implanting into patients vectors or cells capable of producing a biologically-active form of **PAR-1** or a precursor of **PAR-1**, i.e., a molecule that can be readily converted to a biological-active form of **PAR-1** by the body. In one approach cells that secrete **PAR-1** may be encapsulated into semipermeable membranes for **implantation** into a patient. The cells can be cells that normally express **PAR-1** or a precursor thereof or the cells can be transformed to express **PAR-1** or a precursor thereof. It is preferred that the cell be of human origin and that the **PAR-1** be human **PAR-1** when the patient is human. However, the formulations and methods herein can be used for veterinary as well as human. . .

SUMM [0138] In a number of circumstances it would be desirable to determine the levels of **PAR-1** in a patient. The identification of **PAR-1** along with the present report showing expression of **PAR-1** provides the basis for the conclusion that the presence of **PAR-1** serves a normal physiological function related to cell growth and survival. Endogenously produced **PAR-1** may also play a role in certain disease conditions.

SUMM [0139] The term "detection" as used herein in the context of detecting the presence of **PAR-1** in a patient is intended to include the determining of the amount of **PAR-1** or the ability to express an amount of **PAR-1** in a patient, the estimation of prognosis in terms of probable outcome of a disease and prospect for recovery, the monitoring of the **PAR-1** levels over a period of time as a measure of status of the condition, and the monitoring of **PAR-1** levels for determining a preferred therapeutic regimen for the patient.

SUMM [0140] To detect the presence of **PAR-1** in a patient, a sample is obtained from the patient. The sample can be a tissue biopsy sample or a sample of blood, plasma, serum, CSF or the like. **PAR-1** tissue expression is disclosed discussed in Examples 5 and 6. Samples for detecting **PAR-1** can be taken from these tissue. When assessing peripheral levels of **PAR-1**, it is preferred that the sample be a sample of blood, plasma or serum. When assessing the levels of **PAR-1** in the central nervous system a preferred sample is a sample obtained from cerebrospinal fluid or neural tissue.

SUMM [0141] In some instances it is desirable to determine whether the **PAR-1** gene is intact in the patient or in a tissue or cell line within the patient. By an intact **PAR-1** gene it is meant that there are no alterations in the gene such as point mutations, deletions, insertions, chromosomal breakage, chromosomal rearrangements and the like wherein such alteration might alter production of **PAR-1** or alter its biological activity, stability or the like to lead to disease processes. Thus, in one embodiment of the present invention a method is provided for

detecting and characterizing any alterations in the **PAR-1** gene. The method comprises providing an oligonucleotide that contains the **PAR-1** cDNA, genomic DNA or a fragment thereof or a derivative thereof. By a derivative of an oligonucleotide, it is meant. . . that the derived sequence has sufficient sequence complementarily to the sequence from which it is derived to hybridize to the **PAR-1** gene. The derived nucleotide sequence is not necessarily physically derived from the nucleotide sequence, but may be generated in any. . .

SUMM . . . known in the art, this assay determines whether a patient or a particular tissue in a patient has an intact **PAR-1** gene or an **PAR-1** gene abnormality.

SUMM [0143] Hybridization to a **PAR-1** gene would involve denaturing the chromosomal DNA to obtain a single-stranded DNA; contacting the single-stranded DNA with a gene probe. . . mNkd gene sequence; and identifying the hybridized DNA-probe to detect chromosomal DNA containing at least a portion of a human **PAR-1** gene.

SUMM [0145] The **PAR-1** gene probes of the present invention can be DNA or RNA oligonucleotides and can be made by any method known. . .

SUMM [0147] **PAR-1** gene abnormalities can also be detected by using the PCR method and primers that flank or lie within the **PAR-1** gene. The PCR method is well known in the art. Briefly, this method is performed using two oligonucleotide primers which. . .

SUMM [0149] After PCR amplification, the DNA sequence comprising **PAR-1** or a fragment thereof is then directly sequenced and analyzed by comparison of the sequence with the sequences disclosed herein. . .

SUMM [0150] In another embodiment, a method for detecting **PAR-1** is provided based upon an analysis of tissue expressing the **PAR-1** gene. The method comprises hybridizing a polynucleotide to mRNA from a sample of tissue that normally expresses the **PAR-1** gene. The sample is obtained from a patient suspected of having an abnormality in the **PAR-1** gene or in the **PAR-1** gene of particular cells.

SUMM [0151] To detect the presence of mRNA encoding **PAR-1** protein, a sample is obtained from a patient. The sample can be from blood or from a tissue biopsy sample.. . .

SUMM [0153] When using the cDNA encoding **PAR-1** protein or a derivative of the cDNA as a probe, high stringency conditions can be used in order to prevent false positives, that is the hybridization and apparent detection of **PAR-1** nucleotide sequences when in fact an intact and functioning **PAR-1** gene is not present. When using sequences derived from the **PAR-1** cDNA, less stringent conditions could be used, however, this would be a less preferred approach because of the likelihood of. . .

SUMM [0154] In order to increase the sensitivity of the detection in a sample of mRNA encoding the **PAR-1** protein, the technique of reverse transcription/polymerization chain reaction (RT/PCR) can be used to amplify cDNA transcribed from mRNA encoding the **PAR-1** protein. The method of RT/PCR is well known in the art, and can be performed as follows. Total cellular RNA. . . primer. Typically, the primer contains an oligo(dT) sequence. The cDNA thus produced is then amplified using the PCR method and **PAR-1** specific primers. (Belyavsky et al., Nucl. Acid Res. 17:2919-2932, 1989; Krug and Berger, Methods in Enzymology, 152:316-325, Academic Press, NY,. . .

SUMM [0157] The present invention further provides for methods to detect the presence of the **PAR-1** protein in a sample obtained from a patient. Any method known in the art for detecting proteins can be used.. . . which is incorporated by reference). Preferred are binder-ligand immunoassay methods including reacting antibodies with an

epitope or epitopes of the **PAR-1** protein and competitively displacing a labeled **PAR-1** protein or derivative thereof.

SUMM [0158] As used herein, a derivative of the **PAR-1** protein is intended to include a polypeptide in which certain amino acids have been deleted or replaced or changed to modified or unusual amino acids wherein the **PAR-1** derivative is biologically equivalent to **PAR-1** and wherein the polypeptide derivative cross-reacts with antibodies raised against the **PAR-1** protein. By cross-reaction it is meant that an antibody reacts with an antigen other than the one that induced its. . .

SUMM [0160] Polyclonal or monoclonal antibodies to the **PAR-1** protein or an epitope thereof can be made for use in immunoassays by any of a number of methods known. . .

SUMM [0162] Oligopeptides can be selected as candidates for the production of an antibody to the **PAR-1** protein based upon the oligopeptides lying in hydrophilic regions, which are thus likely to be exposed in the mature protein.

SUMM [0164] Methods for preparation of the **PAR-1** protein or an epitope thereof include, but are not limited to chemical synthesis, recombinant DNA techniques or isolation from biological. .

SUMM [0165] Inhibitors of **PAR-1** are Effective in Reducing **PAR-1** Gene Expression

SUMM [0166] Inventive **PAR-1** inhibitors include **antisense** molecules and ribozymes, proteins or polypeptides, antibodies or fragments thereof as well as small molecules. These **PAR-1** inhibitors share the common feature that they reduce the expression and/or biological activity of **PAR-1** and, as a consequence, modulate, inhibit, or prevent the growth of cancer cells. In addition to the exemplary **PAR-1** inhibitors disclosed herein, alternative inhibitors may be obtained through routine experimentation utilizing methodology either specifically disclosed herein or as otherwise. . .

SUMM [0167] **Antisense** Molecules and Ribozymes

SUMM [0168] **PAR-1** inhibitors of the present invention include **antisense** molecules that, when administered to mammalian cells, are effective in reducing, for example, intracellular levels of **PAR-1** mRNA. **Antisense** molecules bind in a sequence-specific manner to nucleic acids, such as mRNA or DNA. When bound to mRNA that has complementary sequences, **antisense** molecules prevent translation of the mRNA (U.S. Pat. No. 5,168,053 to Altman et al.; U.S. Pat. No. 5,190,931 to Inouye,. . . to Burch; U.S. Pat. No. 5,087,617 to Smith and Clusel et al. Nucl. Acids Res. 21:3405-3411 (1993), which describes dumbbell **antisense** oligonucleotides).

SUMM [0169] **Antisense** technology can be used to control gene expression through triple-helix formation, which promotes the ability of the double helix to. . . Gee et al., In Huber and Carr, "Molecular and Immunologic Approaches," Futura Publishing Co. (Mt. Kisco, N.Y.; 1994). Alternatively, an **antisense** molecule may be designed to hybridize with a control region of the **PAR-1** gene, e.g., promoter, enhancer or transcription initiation site, and block transcription of the gene; or block translation by inhibiting binding. . . Biology of RNA: New Perspectives (M. Inouye and B. S. Dudock, eds., 1987 Academic Press, San Diego, p. 401); Oligonucleotides: **Antisense** Inhibitors of Gene Expression (J. S. Cohen, ed., 1989 MacMillan Press, London); Stein and Cheng, Science 261:1004-1012 (1993); WO 95/10607;. . .

SUMM . . . are constructed such that they are complementary to, and able to form Watson-Crick base pairs with, a region of transcribed **PAR-1** mRNA sequence. The resultant double-stranded nucleic acid interferes with subsequent processing of the mRNA, thereby preventing protein synthesis.

SUMM [0171] In general, a portion of a sequence complementary to the **PAR-1** coding region may be used to modulate gene expression. The sequence of **PAR-1** cDNA is presented herein as SEQ ID NOs:1, 2, 4, 5, 7, 8, 10, 11, 19 or 20. Alternatively, cDNA constructs that can be transcribed into **antisense** RNA may be introduced into cells or tissues to facilitate the production of **antisense** RNA. Thus, as used herein, the phrase "**antisense** molecules" broadly encompasses **antisense** oligonucleotides whether synthesized as DNA or RNA molecules as well as all plasmid constructs that, when introduced into a mammalian cell, promote the production of **antisense** RNA molecules. An **antisense** molecule may be used, as described herein, to inhibit expression of mRNA or protein, as well as any other gene that requires **PAR-1** for its expression.

SUMM [0172] The present invention relates to **antisense** oligonucleotides designed to interfere with the normal function of **PAR-1** polynucleotides. Any modifications or variations of the **antisense** molecule which are known in the art to be broadly applicable to **antisense** technology are included within the scope of the invention. Such modifications include preparation of phosphorus-containing linkages as disclosed in U.S.. . .

SUMM [0173] The **antisense** compounds of the invention can include modified bases as disclosed in U.S. Pat. No. 5,958,773 and patents disclosed therein. The **antisense** oligonucleotides of the invention can also be modified by chemically linking the oligonucleotide to one or more moieties or conjugates to enhance the activity, cellular distribution, or cellular uptake of the **antisense** oligonucleotide. Such moieties or conjugates include lipids such as cholesterol, cholic acid, thioether, aliphatic chains, phospholipids, polyamines, polyethylene glycol (PEG),. . .

SUMM [0174] Chimeric **antisense** oligonucleotides are also within the scope of the invention, and can be prepared from the present inventive oligonucleotides using the. . .

SUMM [0175] In the **antisense** art a certain degree of routine experimentation may be required to select optimal **antisense** molecules for particular targets. To be effective, the **antisense** molecule preferably is targeted to an accessible, or exposed, portion of the target RNA molecule. Although in some cases information is available about the structure of target mRNA molecules, the current approach to inhibition using **antisense** is via experimentation. According to the invention, this experimentation can be performed routinely by transfecting cells with an **antisense** oligonucleotide using methods described in Examples 6 and 8. mRNA levels in the cell can be measured routinely in treated. . .

SUMM [0176] Measuring the specificity of **antisense** activity by assaying and analyzing cDNA levels is an art-recognized method of validating **antisense** results. It has been suggested that RNA from treated and control cells should be reverse-transcribed and the resulting cDNA populations. . . A. D., T.I.B.S. 23:45-50, 1998.) According to the present invention, cultures of HT1080 and SW620 cells were transfected with different **antisense** oligonucleotides designed to target **PAR-1**. These oligonucleotides are shown in SEQ ID NOs:13, 15 and 17. The effects of **antisense** treatment are described in Examples 6 and 8.

SUMM [0177] **Antisense** molecules for use as described herein can be synthesized by any method known to those of skill in this art. . . by reference. Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding the **PAR-1** cDNA, or a portion thereof, provided that the DNA is incorporated into a vector downstream of a suitable RNA polymerase promoter (such as, e.g., T3, T7 or SP6). Large amounts of **antisense** RNA may be produced by incubating labeled nucleotides with a linearized **PAR-1** cDNA fragment downstream of such a promoter in the presence of the appropriate RNA polymerase. Such **antisense** molecules are preferably at least 10, 15 or 20

nucleotides in length. More preferably, **antisense** molecules are at least 25 nucleotides in length. Within certain embodiments, an **antisense** molecule of the present invention will comprise a sequence that is unique to the **PAR-1** CDNA sequence of SEQ ID NOs: or that can hybridize to the cDNA of SEQ ID NOs:1, 2, 4, 5,. . .

SUMM [0178] **Antisense** oligonucleotides are typically designed to resist degradation by endogenous nucleolytic enzymes by using such linkages as: phosphorothioate, methylphosphonate, sulfone, sulfate,. . . et al., Tetrahedron 40:137-143 (1984); Eckstein, Annu. Rev. Biochem. 54:367-402 (1985); Eckstein, Trends Biol. Sci. 14:97-100 (1989); Stein, in: Oligodeoxynucleotides. **Antisense** Inhibitors of Gene Expression, Cohen, Ed, Macmillan Press, London, pp. 97-117 (1989); Jager et al., Biochemistry 27:7237-7246 (1988)). Possible additional. . .

SUMM [0179] Within alternate embodiments of the present invention, **PAR-1** inhibitors may be ribozymes. A **ribozyme** is an RNA molecule that specifically cleaves RNA substrates, such as mRNA, resulting in specific inhibition or interference with cellular gene expression. As used herein, the term "ribozymes" includes RNA molecules that contain **antisense** sequences for specific recognition, and an RNA-cleaving enzymatic activity. The catalytic strand cleaves a specific site in a target RNA. . .

SUMM . . . A wide variety of ribozymes may be utilized within the context of the present invention, including for example, the hammerhead **ribozyme** (for example, as described by Forster and Symons, Cell 48:211-220 (1987); Haseloff and Gerlach, Nature 328:596-600 (1988); Walbot and Bruening, Nature 334:196 (1988); Haseloff and Gerlach, Nature 334:585 (1988)); the hairpin **ribozyme** (for example, as described by Haseloff et al., U.S. Pat. No. 5,254,678, issued Oct. 19, 1993 and Hempel et al.,. . .

SUMM . . . 5,144,019; and 5,168,053, 5,180,818, 5,116,742 and 5,093,246 to Cech et al.). According to certain embodiments of the invention, any such **PAR-1** mRNA-specific **ribozyme**, or a nucleic acid encoding such a **ribozyme**, may be delivered to a host cell to effect inhibition of **PAR-1** gene expression. Ribozymes and the like may therefore be delivered to the host cells by DNA encoding the **ribozyme** linked to a eukaryotic promoter, such as a eukaryotic viral promoter, such that upon introduction into the nucleus, the **ribozyme** will be directly transcribed. Proteins and Polypeptides In addition to the **antisense** molecules and ribozymes disclosed herein, **PAR-1** modulators of the present invention also include proteins or polypeptides that are effective in either reducing **PAR-1** gene expression or in decreasing one or more of PAR-i's biological activities. A variety of methods are readily available in the art by which the skilled artisan may, through routine experimentation, rapidly identify such **PAR-1** inhibitors. The present invention is not limited by the following exemplary methodologies.

SUMM [0182] Inhibitors of **PAR-1**'s biological activities encompass those proteins and/or polypeptides that interfere with cell proliferation, particularly tumor cell proliferation, especially colon cell proliferation.. . . to a region that normally binds to another protein. Accordingly, available methods for identifying proteins and/or polypeptides that bind to **PAR-1** may be employed to identify lead compounds that may, through the methodology disclosed herein, be characterized for their **PAR-1** inhibitory activity.

SUMM [0184] Inventive **PAR-1** inhibitors may be identified through biological screening assays that rely on the direct interaction between the **PAR-1** protein and a panel or library of potential inhibitor proteins. Biological screening methodologies, including the various "n-hybrid technologies," are described. . .

SUMM [0185] The two-hybrid screening methodology may be employed to search new or existing target cDNA libraries for **PAR-1** binding proteins that have inhibitory properties. The two-hybrid system

is a genetic method that detects protein-protein interactions by virtue of. . .

SUMM [0187] Suitable bait proteins for the identification of **PAR-1** interacting proteins may be designed based on the **PAR-1** cDNA sequence presented herein as SEQ ID NOs:1, 2, 4, 5, 7, 8, 10, 11, 19 or 20. Such bait proteins include either the full-length **PAR-1** protein or fragments thereof.

SUMM [0188] Plasmid vectors, such as, e.g., pBTM116 and pAS2-1, for preparing **PAR-1** bait constructs and target libraries are readily available to the artisan and may be obtained from such commercial sources as,. . .

SUMM [0189] **PAR-1** modulators of the present invention may alternatively be identified through one of the physical or biochemical methods available in the. . .

SUMM [0190] **PAR-1** is believed to interact with the other cell surface proteins. Through the protein affinity chromatography methodology, lead compounds to be tested as potential **PAR-1** inhibitors may be identified by virtue of their specific retention to **PAR-1** when either covalently or non-covalently coupled to a solid matrix such as, e.g., Sepharose beads. The preparation of protein affinity. . . et al., Methods Enzymol. 208:24-45 (1991). Cell lysates containing the full complement of cellular proteins may be passed through the **PAR-1** affinity column. Proteins having a high affinity for **PAR-1** will be specifically retained under low-salt conditions while the majority of cellular proteins will pass through the column. Such high affinity proteins may be eluted from the immobilized **PAR-1** under conditions of high-salt, with chaotropic solvents or with sodium dodecyl sulfate (SDS). In some embodiments, it may be preferred to radiolabel the cells prior to preparing the lysate as an aid in identifying the **PAR-1** specific binding proteins. Methods for radiolabeling manunalian cells are well known in the art and are provided, e.g., in Sopta,. . .

SUMM [0191] Suitable **PAR-1** proteins for affinity chromatography may be fused to a protein or polypeptide to permit rapid purification on an appropriate affinity. . . containing amylose; and dihydrofolate reductase, which can be purified on methotrexate columns. One exemplary tag suitable for the preparation of **PAR-1** fusion proteins that is presented herein is the epitope for the influenza virus hemaglutinin (HA) against which monoclonal antibodies are. . .

SUMM [0192] Proteins that are specifically retained on a **PAR-1** affinity column may be identified after subjecting to SDS polyacrylamide gel electrophoresis (SDS-PAGE). Thus, where cells are radiolabeled prior to the preparation of cell lysates and passage through the **PAR-1** affinity column, proteins having high affinity for **PAR-1** may be detected by autoradiography. The identity of **PAR-1** specific binding proteins may be determined by protein sequencing techniques that are readily available to the skilled artisan, such as. . .

SUMM [0194] **PAR-1** modulators (antagonists and agonists) of the present invention include antibodies and/or antibody fragments that are effective in modulating **PAR-1** gene expression and/or biological activity. Suitable antibodies may be monoclonal, polyclonal or humanized monoclonal antibodies. Antibodies may be derived by conventional hybridoma based methodology, from antisera isolated from **PAR-1** inoculated animals or through recombinant DNA technology. Alternatively, inventive antibodies or antibody fragments may be identified in vitro by use. . .

SUMM . . . animals by injecting antigen followed by subsequent boosts at appropriate intervals. The animals are bled and sera assayed against purified **PAR-1** protein usually by ELISA or by bioassay based upon the ability to block the action of **PAR-1**. In a non-limiting example, an antibody to **PAR-1** can block the binding of **PAR-1** to

Dishevelled protein. When using avian species, e.g., chicken, turkey and the like, the antibody can be isolated from the. . .

SUMM . . . Thus, another aspect of the present invention provides for a method for preventing or treating diseases involving overexpression of the **PAR-1** protein by treatment of a patient with specific antibodies to the **PAR-1** protein.

SUMM [0197] Specific antibodies, either polyclonal or monoclonal, to the **PAR-1** protein can be produced by any suitable method known in the art as discussed above. For example, murine or human monoclonal antibodies can be produced by hybridoma technology or, alternatively, the **PAR-1** protein, or an immunologically active fragment thereof, or an anti-idiotypic antibody, or fragment thereof can be administered to an animal to elicit the production of antibodies capable of recognizing and binding to the **PAR-1** protein. Such antibodies can be from any class of antibodies including, but not limited to IgG, IgA, IgM, IgD, and. . .

SUMM [0198] In one embodiment of the present invention, **PAR-1** modulators are monoclonal antibodies that may be produced as follows. **PAR-1** protein may be produced, for example, by expression of **PAR-1** cDNA in a baculovirus based system. By this method, **PAR-1** cDNA or a fragment thereof is ligated into a suitable plasmid vector that is subsequently used to transfect Sf9 cells. . . In addition, it may be advantageous to incorporate an epitope tag or other moiety to facilitate affinity purification of the **PAR-1** protein. Clones of Sf9 cells expressing **PAR-1** are identified, e.g., by enzyme linked immunosorbant assay (ELISA), lysates are prepared and the **PAR-1** protein purified by affinity chromatography and the purified protein is injected, intraperitoneally, into BALB/c mice to induce antibody production. It. . .

SUMM . . . to generate hybridoma clones. Supernatants derived from hybridoma clones are tested for the presence of monoclonal antibodies having specificity against **PAR-1**. For a general description of monoclonal antibody methodology, see, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor. . .

SUMM . . . addition to the baculovirus expression system, other suitable bacterial or yeast expression systems may be employed for the expression of **PAR-1** protein or polypeptides thereof. As with the baculovirus system, it may be advantageous to utilize one of the commercially available affinity tags to facilitate purification prior to inoculation of the animals. Thus, the **PAR-1** cDNA or fragment thereof may be isolated by, e.g., agarose gel purification and ligated in frame with a suitable tag. . .

SUMM [0201] In other embodiments of the present invention, **PAR-1** modulators are humanized anti-**PAR-1** monoclonal antibodies. The phrase "humanized antibody" refers to an antibody derived from a non-human antibody--typically a mouse monoclonal antibody. Alternatively,. . .

SUMM [0207] In the present invention, **PAR-1** polypeptides of the invention and variants thereof are used to immunize a transgenic animal as described above. Monoclonal antibodies are made using methods known in the art, and the specificity of the antibodies is tested using isolated **PAR-1** polypeptides.

SUMM [0208] It will be appreciated that alternative **PAR-1** inhibitor antibodies may be readily obtained by other methods commonly known in the art. One exemplary methodology for identifying antibodies having a high specificity for **PAR-1** is the phage display technology.

SUMM [0211] **PAR-1** protein suitable for screening a phage library may be obtained by, for example, expression in baculovirus Sf9 cells as described, supra. Alternatively, the **PAR-1** coding region may be PCR amplified using primers specific to the desired region of the **PAR-1** protein. As discussed above, the **PAR-1** protein may be expressed in E. coli or yeast as

a fusion with one of the commercially available affinity tags.

SUMM . . . then be adsorbed to a solid matrix, e.g., a tissue culture plate or bead. Phage expressing antibodies having the desired anti-**PAR-1** binding properties may subsequently be isolated by successive panning, in the case of a solid matrix, or by affinity adsorption to a **PAR-1** antigen column. Phage having the desired **PAR-1** inhibitory activities may be reintroduced into bacteria by infection and propagated by standard methods known to those skilled in the. . .

SUMM [0214] The present invention also provides small molecule **PAR-1** modulators (antagonists and agonists) that may be readily identified through routine application of high-throughput screening (HTS) methodologies. Persidis, A., Nature. . .

SUMM [0216] HTS methodology may be employed, e.g., to screen for lead compounds that block one of **PAR-1**'s biological activities, particularly its binding to Dsh/Dvl. By this method, **PAR-1** protein may be immunoprecipitated from cells expressing the protein and applied to wells on an assay plate suitable for robotic. . .

SUMM [0217] Methods for Assessing the Efficacy of **PAR-1** Modulators

SUMM [0218] Lead molecules or compounds, whether **antisense** molecules or ribozymes, proteins and/or peptides, antibodies and/or antibody fragments or small molecules, that are identified either by one of. . . in a variety of in vitro, ex vivo and in vivo animal model assay systems for their ability to inhibit **PAR-1** gene expression or biological activity. As discussed in further detail in the Examples, **PAR-1** inhibitors of the present invention are effective in reducing **PAR-1** expression levels and inhibiting cancer cell proliferation. Thus, the present invention further discloses methods that permit the skilled artisan to. . .

SUMM [0219] As noted above and as presented in the Examples, candidate **PAR-1** inhibitors may be tested by administration to cells that either express endogenous **PAR-1** or that are made to express **PAR-1** by transfection of a mammalian cell, such as SW620, with a recombinant **PAR-1** plasmid construct.

SUMM [0220] Effective **PAR-1** inhibitory molecules will reduce the levels of **PAR-1** mRNA as determined, e.g., by Northern blot or RT-PCR analysis. Example 1; Sambrook et al., Molecular Cloning: A Laboratory Manual. . . Press (ed. Glick, B. R. and Pasternak, J. J. 1998) incorporated herein by reference, or may reduce the levels of **PAR-1** protein in the cell. The effectiveness of a given candidate **antisense** molecule may be assessed by comparison with a control "**antisense**" molecule known to have no substantial effect on **PAR-1** expression when administered to a mammalian cell. Exemplary control molecules include the RC oligonucleotides disclosed in Example 2.

SUMM [0221] **PAR-1** inhibitors effective in reducing **PAR-1** gene expression and/or cell proliferation by one or more of the methods discussed herein may be further characterized in vivo. . .

SUMM [0222] Administration of **PAR-1** Inhibitors and Compositions Thereof

SUMM [0223] The present invention provides **PAR-1** inhibitors and compositions comprising one or more **PAR-1** inhibitor as well as methods that employ these inventive inhibitors in in vivo, ex vivo, and in vitro applications where it is advantageous to reduce or eliminate the expression or activity of **PAR-1** or a functionally downstream molecule. **PAR-1** inhibitors may find use as drugs for supplementing cancer therapeutics and other agents. **PAR-1** inhibitors may also find use in other diseases of hyperproliferation.

SUMM [0225] Inventive compositions will include one or more **PAR-1** inhibitor and may further comprise a pharmaceutically acceptable carrier or excipient. A variety of aqueous carriers may be used, e.g.,. . .

SUMM [0226] **PAR-1** inhibitors useful in the treatment of disease in mammals will often be prepared substantially free of other naturally occurring immunoglobulins or other biological molecules. Preferred **PAR-1** inhibitors will also exhibit minimal toxicity when administered to a mammal.

SUMM [0228] The selection of the appropriate method for administering **PAR-1** inhibitors of the present invention will depend on the nature of the application envisioned as well as the nature of the **PAR-1** inhibitor. Thus, for example, the precise methodology for administering a **PAR-1** inhibitor will depend upon whether it is an **antisense** molecule, a protein and/or peptide, an antibody or antibody fragment or a small molecule. Other considerations include, for example, whether the **PAR-1** inhibitor will be used to inhibit tumor cell growth, invasion, or metastasis, or as an adjunct to other cancer therapeutics.

SUMM [0229] A variety of methods are available in the art for the administration of **antisense** molecules. Exemplary methods include gene delivery techniques, including both viral and non-viral based methods as well as liposome mediated delivery. . .

SUMM [0231] Alternatively, gene delivery methodology may be used to directly knock out endogenous **PAR-1** within tumor cells. For example, the **PAR-1** gene may be targeted by transfection of a gene delivery vector carrying a **PAR-1** inhibitor. Preferential transfection into or expression within tumor cells may be achieved through use of a tissue-specific or cell cycle-specific. . .

SUMM [0232] Thus, to achieve therapeutic benefit, **PAR-1** within the tumor cells should be preferentially inhibited. This can be accomplished by transfecting a gene expressing a **PAR-1** inhibitor, a **PAR-1 antisense** molecule, a **PAR-1** gene specific repressor, or an inhibitor of the protein product of the **PAR-1** gene.

SUMM . . . generally to a nucleic acid construct that carries and, within certain embodiments, is capable of directing the expression of an **antisense** molecule of interest, as described in, for example, Molecular Biotechnology: Principles and Applications of Recombinant DNA, Ch. 21, pp. 555-590. . .

SUMM . . . number of virus and non-virus based gene delivery vector systems have been described that are suitable for the administration of **PAR-1** inhibitors. Virus based gene delivery systems include, but are not limited to retrovirus, such as Moloney murine leukemia virus, spumaviruses. . .

SUMM . . . one aspect of the present invention, retroviral gene delivery vectors are provided that are constructed to carry or express a **PAR-1** inhibitory **antisense** molecule. As used herein, the term "**PAR-1** inhibitory **antisense** molecule" refers generally to a nucleic acid sequence having **PAR-1** inhibitory activity. More specifically, such **antisense** molecules will reduce **PAR-1** gene expression. Retroviral gene delivery vectors of the present invention may be readily constructed from a wide variety of retroviruses,. . .

SUMM [0239] A retroviral vector, suitable for the expression of a **PAR-1** inhibitory **antisense** molecule, must include at least one transcriptional promoter/enhancer or locus defining element(s), or other elements that control gene expression by. . .

SUMM . . . that make them particularly suitable for the development of gene delivery vectors generally and for the delivery of polynucleotides encoding **PAR-1** inhibitory **antisense** molecules in particular. For a general review of AAV expression systems, see Rabinowitz et al., Current Opin. Biotech. 9(5):470-475 (1998).. . .

SUMM [0244] A variety of AAV gene delivery vectors may be utilized to direct the expression of one or more **PAR-1** inhibitor **antisense** molecule. Representative examples of such vectors include the AAV vectors disclosed by Srivastava in WO 93/09239; Samulski, et al. J.. . .

SUMM . . . of the present invention may include, in order, a 5' adeno-associated virus inverted terminal repeat; a polynucleotide encoding the PAR-1inhibitory **antisense** molecule; a sequence operably linked to the **PAR-1** inhibitory **antisense** molecule that regulates its expression in a target tissue, organ or cell; and a 3' adeno-associated virus inverted terminal repeat. A suitable regulatory sequence for the expression of **PAR -1** inhibitory **antisense** molecule is, e.g., the enhancer/promoter sequence of cytomegalovirus (CMV). In addition, the AAV vector may preferably have a polyadenylation sequence. . .

SUMM [0247] Generally, AAV vectors should have one copy of the AAV ITR at each end of the **PAR-1** inhibitory **antisense** molecule, to allow replication, packaging, efficient integration into the host cell genome and rescue from the chromosome. The 5' ITR. . .

SUMM . . . total size of the nucleic acid sequence between the two ITRs to between 2 and 5 kb. Thus, where the **PAR-1** inhibitory **antisense** molecule is smaller than 2-5 kb, a non- coding stuffer polynucleotide may be incorporated, for example, 3' to the 5' ITR sequence and 5' of the **PAR-1** inhibitory **antisense** molecule. The precise nucleotide sequence of the stuffer fragment is not an essential element of the final construct.

SUMM [0249] Depending upon the precise application contemplated, rather than incorporating a stuffer fragment, multiple copies of the **PAR-1** inhibitory **antisense** molecule may be inserted, inter alia, to achieve the optimal ITR sequence spacing. It may be preferred to organize the. . .

SUMM [0251] Within certain embodiments of the invention, expression of the **PAR-1** inhibitory **antisense** molecule may be accomplished by a separate promoter (e.g., a viral promoter). Representative examples of suitable promoters in this regard. . .

SUMM . . . packaging cell lines may contain both an AAV helper virus as well as an AAV gene delivery vector containing the **PAR-1** inhibitory **antisense** molecule. For detailed descriptions of representative packaging cell line systems, see, e.g. Holscher, C. et al., J. Virol. 68:7169-7177 (1994);. . .

SUMM . . . to obviate transfection protocols or packaging cell lines. Such in vitro systems incorporate an AAV gene delivery vector bearing the **PAR-1** inhibitory **antisense** molecule and a source of Rep-protein, capsid-protein and Adenovirus proteins that supply helper-viral functions. The latter proteins are typically supplied. . .

SUMM . . . vectors and adeno-associated virus-based vectors, numerous other viral gene delivery vector systems may also be utilized for the expression of **PAR-1** inhibitory **antisense** molecules. For example, within one embodiment of the invention adenoviral vectors may be employed. Representative examples of such vectors include. . .

SUMM [0261] Other gene delivery vectors and methods that may be employed for the expression of **PAR-1** inhibitory **antisense** molecules such as, for example, nucleic acid expression vectors; polycationic condensed DNA linked or unlinked to killed adenovirus alone, for. . .

SUMM [0262] Particle mediated gene delivery may be employed. Briefly, the **PAR-1** inhibitory **antisense** molecule of interest can be inserted into conventional vectors that contain conventional control sequences for high level expression, and then. . .

SUMM [0266] The polynucleotides of the invention can be formulated as a diagnostic kit for detecting, for example, the expression of **PAR -1** messenger RNA in a tumor cell. A diagnostic kit may contain

at least one oligonucleotide capable of hybridizing to SEQ. . .

SUMM [0267] **PAR-1** may also be used in screens to identify drugs for treatment of cancers which involve over-activity of the encoded protein,. . .

SUMM [0268] For all of the preceding embodiments, the clinician will determine, based on the specific condition, whether **PAR-1** polypeptides or polynucleotides, antibodies to **PAR-1**, or small molecules such as peptide analogues or antagonists, will be the most suitable form of treatment. These forms are. . .

DETD Isolation Of **PAR-1** from Drosophila

DETD . . . encodes the kinase was cloned. The cDNA clones encode a protein kinase that is homologous to the C. elegans protein **PAR-1** (85% identity in the kinase domain and 42% identity overall). This indicates that the Dsh-associated kinase is a **PAR-1** homolog and was designated dPAR-1. Importantly, the kinase activity that was precipitated using GST-DM increased as Dsh became progressively phosphorylated. . .

DETD . . . Clone-8 cells with an affinity purified Dsh antibody and dPAR-1 was detected in the immunocomplex by Western blot using a **PAR-1** antibody. The cells were lysed as described above. This confirms the observation that **PAR-1** activity was physically associated with Dsh in Drosophila embryos and cells.

DETD Isolation of Human **PAR-1**

DETD . . . human fetal and adult brain. They were cloned into pcDNA3.1 (Invitrogen) with a Myc tag added at C-terminus. All three **hPAR-1** were found to be widely expressed in various tissues, including brain, fetal brain, colon, prostate, breast, ovary, and testis.

DETD [0277] The sequences for the human (h) and Drosophila (d) **PAR-1** forms are provided in the Sequence Listing as follows:

SEQ ID NO:1 and 2: hPAR-1A DNA sequence

SEQ ID NO:3:. . .

DETD Modulation of WNT Signaling by **PAR-1**

DETD [0280] To investigate if **PAR-1** is involved in Wnt signaling, **PAR-1** activity was examined in the Drosophila wing imaginal disc cell line Clone-8 cells after stimulation with conditioned medium containing Wingless. . . cells confirmed that Dsh became phosphorylated, and Armadillo (Arm), a Drosophila homolog of .beta.-catenin, was stabilized. The kinase activity of **PAR-1** was also measured under the same conditions. Multiple experiments showed that although dPAR-1 specific activity increased in cells treated with soluble Wg, there was no change in the amount of **PAR-1** protein that interacted with GST-DM5. Thus, treatment of cells with Wg increased the specific activity of **PAR-1**. The increased **PAR-1** activity correlated with enhanced Dsh phosphorylation and increased Arm levels in Clone-8 cells. These experiments also indicate that the kinase activity detected is specific to **PAR-1**, since an anti-dPAR-1 antibody treatment of lysates before the assay depleted the kinase activity of Clone-8 cell lysates.

DETD . . . good expression from transfected DNA and these cells have a well-characterized response to Wnt. Duplicate transfections with luciferase reporters and **PAR-1** cDNAs (test CDNA) were carried out using Superfect (Qiagen). 24-26 hours after transfection, the cells were lysed and luciferase activities. . .

DETD [0282] All three **PAR-1** strongly potentiated Wnt1 or mouse Dvl-3 mediated CRT activation in mammalian (CHO) cells. Mouse Dvl-3 (Tsang 96) was PCR amplified. . . added at C-terminus. Expression of an unrelated protein, such as GST, had no effect on Wnt1-induced CRT in mammalian cells. **PAR-1** did not activate the CRT on its own, but instead required coexpression of Wnt or Dvl to activate CRT. This indicates that interactions with components of Wnt signaling are required for **PAR-1** function. It

was found that **PAR-1** did not affect CRT induced by overexpression of .beta.-catenin in cells.

DETD . . . the JNK MAPK pathway. LEF1 is a downstream transcription factor required for CRT activation in the Wnt pathway. In addition, **PAR-1** also diminished the Dvl-3-mediated JNK activation.

DETD Mutant **PAR-1** Blocks Phosphorylation of DSH/DVL in Cells Stimulated with WNT

DETD [0284] To determine whether **PAR-1** is required for the Wnt pathway in mammalian cells, kinase-negative **PAR-1** (**PAR-1** KN) was expressed to suppress endogenous **PAR-1** activity in mammalian (CHO) cells to examine if it could block Wnt signaling. The kinase mutants were generated by converting. . .

DETD . . . as shown by the reduced amount of a retarded Dvl band. This result is consistent with the data showing that **PAR-1** phosphorylates Dsh in vitro and in cells.

DETD [0287] Further it was determined that both human and Drosophila **PAR-1** KN strongly suppressed Wnt-induced .beta.-catenin stabilization. However, neither was able to inhibit the gene response mediated by overexpression of .beta.-catenin. In addition, overexpression of a peptide from Dvl-3 consisting of the **PAR-1**-binding region of Dsh in CHO cells inhibited the ability of Wnt1 to activate CRT, whereas it had no effect on .beta.-catenin-induced CRT activation. These results indicate that **PAR-1** regulates Wnt signaling in a step upstream of P-catenin consistent with the finding that **PAR-1** interacts with and phosphorylates Dsh/Dvl.

DETD [0288] To test the specificity of the effects of **PAR-1** KN, the HPAR KN (PAR-1B.alpha. KN) was coexpressed with wild type hPAR (PAR-1B.alpha.) in the CHO cells. The coexpression completely blocked the inhibitory effects of hPAR KN. These results support the conclusion that the kinase negative **PAR-1** affects Wnt signaling by specifically interfering with endogenous **PAR-1** activity in the cells.

DETD [0289] As disclosed in Example 4, over-expression of **PAR-1** diminished the Dvl-3-mediated JNK activation. It was further determined that this inhibitory effect was dependent on the kinase activity of **PAR-1** since co-expression of a dominant negative **HPAR-1** KN lead to the loss of inhibitory effect on JNK activation. These data indicate that **PAR-1** promotes Dsh/Dvl function in the Wnt/.beta.-catenin pathway but suppresses Dsh function in the JNK pathway, thereby acting as a switch.

DETD **PAR-1 Antisense** Oligonucleotides Suppress Wnt Responses in Human Cells

DETD [0290] **Antisense** oligonucleotides were used to reduce endogenous **PAR-1** protein levels in human cell line HT1080, which expresses all three **PAR-1** forms. HT1080 cells were used because **antisense** oligonucleotides can be delivered to these cells with relative ease and also HT1080 cells have a very robust transcriptional response to Wnt. The **antisense** or control oligonucleotides (final concentration of 100-200 nm) were transfected into HT1080 cells using cationic peptoid reagents as described in. . . (1998). The cells were lysed 44 hours later and blotted with anti-PAR-12 antibody. The oligonucleotides used were as follows:

PAR-1A: **antisense** (5'-CGTATGGAGGACTGCCACAAAACGT-3') (SEQ ID NO:13) and
control (5'-TGCAAAACACCGTCAGGAGGTATGC-3' (SEQ ID NO:14);

PAR-1B: **antisense** (5'-TGAGGTCTGAGCGTCTCCACTCGG-3') (SEQ ID NO:15) and
control (5'-GGCTCACCTCTGCGAGTCTGGAGT-3') (SEQ

ID NO:16); and

PAR-1C: **antisense** (5'-GAGAATGACGCCCAGACTCCACACA-3') (SEQ ID NO:17) and
control (5'-ACACACCTCAGACCCGCAGTAAGAG-3') (SEQ ID NO:18).

DETD [0291] The **antisense** oligonucleotides specifically reduced these target messenger by 75-90% but control oligonucleotides had no effect. The **antisense** oligonucleotides also significantly reduced endogenous **PAR-1** protein levels but the control oligonucleotides had no effect on them. A cellular protein unrelated to **PAR-1**, tubulin, was not affected by the **antisense** oligonucleotides.

DETD [0292] HT1080 cells were also transfected with an individual **PAR-1 antisense** oligonucleotide as indicated above and cells were lysed about 30 hours later. **PAR-1** activity was measured by precipitation with GST fusion protein containing the 36 amino acid residues PAR-1binding fragment from Dv13 and followed by an in vitro kinase assay. Each **PAR-1 antisense** oligonucleotide reduced **PAR-1** kinase activity in cells, supporting the observation that they all interact and phosphorylate Dvl. Knocking out individual **PAR-1** by single **antisense** oligonucleotide resulted in a 25-40% reduction of Wnt signaling in the cells but the control oligonucleotides had minimal effects on. . .

DETD . . . measured 24 hours later after that. The CRT activation was obtained as described in Example 4. Simultaneously knocking out two **PAR-1** with two **antisense** oligos resulted in further reduction, up to 60%, in Wnt response, indicating the existence of synergy among three endogenous **PAR-1** in the Wnt pathway. The partial inhibition of Wnt response after **antisense** treatment also indicated that these three **PAR-1** play a redundant role in Wnt signaling in the cells.

DETD Suppression of **PAR-1** Inhibits Wnt Signaling in Xenopus

DETD [0294] The role of **PAR-1** in Wnt signaling in vertebrates was examined by injecting **PAR-1** mRNA into Xenopus embryos. For Xenopus RNA injection, PAR-1B.alpha. WT, PAR-1B.alpha. KN, PAR-1A KN and green fluorescent protein (GFP) were. . .

DETD . . . stage blastomeres. The injected embryos were scored for axis duplication at 72 hours. To evaluate suppression effect of dominant negative **PAR-1**, injected embryos were scored as no duplication (0), partial duplication (1), or second axis with a head and cement gland. . . a similar dose of green fluorescent protein (GFP)-RNA had no effect. This inhibition was partially rescued by co-expression of wild-type **PAR-1** B.alpha. or dPAR-1, respectively. At the same dose, PAR-1B.alpha. KN alone had no effect on development when injected into the. . .

DETD **PAR-1 Antisense** Suppresses Cancer Cell Foci Formation

DETD [0296] To characterize **hPAR-1**'s role in tumorigenicity, hPAR-1s were tested for their function in a soft agar (anchorage-independent) assay. The cells used in this. . . protein due to a mutation in the tumor suppressor APC gene. SW620 cells were treated with the hPAR-1A or hPAR1-C **antisense** oligonucleotides or reverse control oligonucleotides of Example 6 and seeded in growth medium containing 0.3% agar in dishes. Colonies formed. . . weeks. Fields of colonies were counted by eye. It was found that treatment of the cells with the HPAR-1A or **HPAR-1**-C **antisense** oligonucleotides significantly reduced the number of colonies as compared to treatment with the reverse control oligonucleotides. These results indicate that **PAR-1** is involved in maintaining a cancer phenotype.

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 13
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **Antisense** oligonucleotide
SEQUENCE: 13
cgtatggagg actgccacaa aacgt 25
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 14
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **Antisense** oligonucleotide
SEQUENCE: 14
tgcaaaacac cgtcaggagg tatgc 25
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 15
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **Antisense** oligonucleotide
SEQUENCE: 15
tgaggtctga gcgtctccac tcgg 24
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 16
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **Antisense** oligonucleotide
SEQUENCE: 16
ggctcacctc tgcgagtctg gagt 24
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 17
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **Antisense** oligonucleotide
SEQUENCE: 17
gagaatgacg cccagactcc acaca 25
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 18
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **Antisense** oligonucleotide
SEQUENCE: 18
acacacctca gacccgcagt aagag 25
CLM What is claimed is:

14. An isolated **PAR-1** modulator selected from the group consisting of an **antisense** oligonucleotide, a **ribozyme**, a protein, a polypeptide, and a small molecule.

15. The isolated **PAR-1** modulator of claim 14, wherein said PAR-1modulator is an **antisense** molecule or the complement thereof.

16. The isolated **PAR-1** modulator of claim 15, wherein said **antisense** molecule or the complement thereof has at least 15 consecutive nucleic acids of the sequence of SEQ ID NO:3,

SEQ. . .
17. The isolated **PAR-1** modulator of claim 15, wherein said **antisense** molecule is selected from the group consisting of SEQ ID NO:13, SEQ ID NO:15 and SEQ ID NO:17.

18. The isolated **PAR-1** modulator of claim 14, wherein said **PAR-1** modulator is selected from the group consisting of an antibody and an antibody fragment.

19. The isolated **PAR-1** modulator of claim 14, wherein said polypeptide has an amino sequence with at least 95% identity to the amino acid. . .
21. A method of treating a mammal with a disease or disorder associated with a **PAR-1** polypeptide, comprising administering to the mammal a composition including a therapeutically effective amount of a **PAR-1** modulator of claim 14.
22. The method of claim 23, wherein said **PAR-1** modulator is an **antisense** molecule is selected from the group consisting of SEQ ID NO:13, SEQ ID NO:15 and SEQ ID NO:17.

23. The method of claim 21, wherein said **PAR-1** modulator is a polypeptide that has an amino sequence with at least 95% identity to the amino acid sequence provided. . .
24. The method of claim 21, wherein said **PAR-1** modulator is selected from the group consisting of an antibody and an antibody fragment.

25. The method of claim 21, wherein said **PAR-1** modulator is administered ex vivo to said mammalian cell.

L14 ANSWER 13 OF 70 USPATFULL

ACCESSION NUMBER:	2002:206605 USPATFULL
TITLE:	Novel nucleic acids and polypeptides
INVENTOR(S):	Tang, Y. Tom, San Jose, CA, UNITED STATES Zhou, Ping, Cupertino, CA, UNITED STATES Goodrich, Ryle, San Jose, CA, UNITED STATES Liu, Chenghua, San Jose, CA, UNITED STATES Asundi, Vinod, Foster City, CA, UNITED STATES Wang, Jian-Rui, Cupertino, CA, UNITED STATES Wang, Dunrui, Poway, CA, UNITED STATES Yamazaki, Victoria, Redwood Shores, CA, UNITED STATES Ujwal, Manusha L., Gaithersburg, MD, UNITED STATES Drmanac, Radoje T., Palo Alto, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002111302	A1	20020815	
APPLICATION INFO.:	US 2000-728952	A1	20001130	(9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Ivor R. Elrifi, Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C, One Financial Center, Boston, MA, 02111
NUMBER OF CLAIMS:	28
EXEMPLARY CLAIM:	1
LINE COUNT:	4863

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . such polypeptides, including recombinant DNA molecules, cloned genes or degenerate variants thereof, especially naturally occurring variants such as allelic variants, **antisense** polynucleotide molecules, and antibodies that specifically recognize one or more epitopes present on such polypeptides, as well as hybridomas producing. . .
SUMM . . . or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the

antisense strand, to peptide nucleic acid (PNA) or to any DNA-like or RNA-like material. In the sequences herein A is adenine,. . .

SUMM . . . inhibiting the activity of polypeptides of the invention will be useful in treating the disease states. It is contemplated that **antisense** therapy or gene therapy could be applied to negatively regulate the expression of polypeptides of the invention.

SUMM [0126] Other methods inhibiting expression of a protein include the introduction of **antisense** molecules to the nucleic acids of the present invention, their complements, or their translated RNA sequences, by methods known in. . .

SUMM . . . directly or indirectly activate or inhibit the polypeptides of the invention (identified, e.g., via drug screening assays as described herein); **antisense** polynucleotides and polynucleotides suitable for triple helix formation; and in particular antibodies or other binding partners that specifically recognize one. . .

SUMM . . . has important working applications for the production of human proteins which currently must be obtained from non-human sources or donors, **implantation** of cells to treat diseases such as Parkinson's, Alzheimer's and other neurodegenerative diseases; tissues for grafting such as bone marrow,. . .

SUMM . . . can also be genetically altered for gene therapy purposes and to decrease host rejection of replacement tissues after grafting or **implantation**.

SUMM . . . B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an **antisense** construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected. . .

SUMM [0266] The compositions (including polypeptide fragments, analogs, variants and antibodies or other binding partners or modulators including **antisense** polynucleotides) of the invention have numerous applications in a variety of therapeutic methods. Examples of therapeutic applications include, but are. . .

SUMM . . . described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by **implantation** (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric. . .

SUMM . . . fragments of the present invention, as broadly described, can be used to control gene expression through triple helix formation or **antisense** DNA or RNA, both of which methods are based on the binding of a polynucleotide sequence to DNA or RNA.. . . 6:3073 (1979); Cooney et al., Science 15241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (**antisense** --Olmno, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while **antisense** RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an **antisense** or triple helix oligonucleotide.

SUMM . . . peptide sequence, in order to generate rationally designed antipeptide peptides, for example see Hurby et al., Application of Synthetic Peptides: **Antisense** Peptides, "In Synthetic Peptides, A User's Guide, W. H. Freeman, NY (1992), pp. 289-307, and Kaspczak et al., Biochemistry 28:9230-8. . .

SUMM . . . 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (**antisense**--Okano, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while **antisense** RNA hybridization blocks translation of an mRNA

molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an **antisense** or triple helix oligonucleotide and other DNA binding agents.

DETD . . . 50 54 60 90

adult liver	Clontech	ALV003	64
adult ovary	Invitrogen	AOV001	3-6 12 20-24 45-47 50-51 57 60 64-65 85 93
placenta	Invitrogen	APL002	51
adult spleen	GIBCO	ASP001	15 45 50 58 69-70
testis	GIBCO	ATS001	31 51 61 64
adult bladder	Invitrogen	BLD001. . .	50-51 54 58 62-65 79
#CRL 1424 induced neuron cells	Strategene	NTD001	49
neuronal cells	Strategene	NTU001	2 31 49 80
pituitary gland	Clontech	PIT004	54
placenta	Clontech	PLA003	19 26 50 71-73
rectum	Invitrogen	REC001	15 29-31 69-70 76 81
salivary gland	Clontech	SAL001	47
small intestine	Clontech	SIN001. . .	

DETD . . . SIGNATURE

89	DM01803 3.625e-06 43-68	1 HERPESVIRUS GLYCOPROTEIN H.	DM01803J 12.93
90	DM01803 3.625e-06 149-174	1 HERPESVIRUS GLYCOPROTEIN H.	DM01803J 12.93
91	PR00908 PR00908F 8.01 1.000e-05 45-64	**THROMBIN RECEPTOR** SIGNATURE	
92	PD02863 9.927e-06 19-63	ELECTRON TRANSPORT HEME PROTEIN C.	PD02863B 19.74
93	DM00060	338 kw NEUREXIN	DM00060. . .

L14 ANSWER 14 OF 70 USPATFULL

ACCESSION NUMBER:	2002:191522 USPATFULL
TITLE:	G protein coupled receptor kinase 5 (GRK5) and its uses
INVENTOR(S):	Delaney, Allen, Vancouver, CANADA Yoganathan, Thillainathan, Richmond, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002102587	A1	20020801
APPLICATION INFO.:	US 2001-972694	A1	20011004 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2001-US21479, filed on 20 Sep 2001, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-237423P	20001002 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	PAMELA J. SHERWOOD, Bozicevic, Field and Francis LLP, Suite 200, 200 Middlefield Road, Menlo Park, CA, 94025
NUMBER OF CLAIMS:	15
EXEMPLARY CLAIM:	1
LINE COUNT:	1356

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . its homology with other members of the GRK family. It is expressed in a number of different tissues, including heart, **placenta** and lung. Autophosphorylation of GRK5 appears to

activate the kinase (Pronin and Benovic (1997) P.N.A.S. 272:3806-3812). GRK5 is also phosphorylated. . .

SUMM [0009] In addition, G protein-coupled receptor kinases appear to play a key role in inactivating **PAR-1**, itself a G protein-coupled receptor (Tiruppathi et al. (2000) P.N.A.S. 97:7440-7445). Phosphorylation of serine/threonine sites by GRKs in the COOH terminus of **PAR-1** has been linked to the mechanism of desensitization of **PAR-1**. GRK5 overexpression inhibits thrombin-activated signaling and expression of a dominant negative GRK5 mutant prolongs thrombin-activated Ca++ signaling in endothelial cells.

SUMM . . . normal tissue of the patient, especially those that express the polynucleotide-related gene of interest (e.g., brain, thymus, testis, heart, prostate, **placenta**, spleen, small intestine, skeletal muscle, pancreas, and the mucosal lining of the colon, etc.). A difference between the polynucleotide-related gene,. . .

SUMM . . . absent or where multiple copies are present and abnormally high levels of expression are present. Specific constructs of interest include **antisense** GRK5, which will block GRK5 expression and expression of dominant negative GRK5 mutations. A detectable marker, such as lac Z. . .

SUMM . . . may be localized by the use of an implant that acts to retain the active dose at the site of **implantation**.

SUMM . . . agents are useful in reducing GRK5 activity, including agents that directly modulate GRK5 expression as described above, e.g. expression vectors, **antisense** specific for GRK5; and agents that act on the GRK5 protein, e.g. GRK5 specific antibodies and analogs thereof, small organic. . .

SUMM . . . effect on a number of proliferative disorders, including inflammation, restenosis, and cancer. Inhibition is achieved in a number of ways. **Antisense** GRK5 sequences may be administered to inhibit expression. Pseudo-substrate inhibitors, for example, a peptide that mimics a substrate for GRK5. . .

SUMM [0088] **Antisense** molecules can be used to down-regulate expression of GRK5 in cells. The **antisense** reagent may be **antisense** oligonucleotides (ODN), particularly synthetic ODN having chemical modifications from native nucleic acids, or nucleic acid constructs that express such **antisense** molecules as RNA. The **antisense** sequence is complementary to the mRNA of the targeted gene, and inhibits expression of the targeted gene products. **Antisense** molecules inhibit gene expression through various mechanisms, e.g. by reducing the amount of mRNA available for translation, through activation of RNAse H, or steric hindrance. One or a combination of **antisense** molecules may be administered, where a combination may comprise multiple different sequences.

SUMM [0089] **Antisense** molecules may be produced by expression of all or a part of the target gene sequence in an appropriate vector, where the transcriptional initiation is oriented such that an **antisense** strand is produced as an RNA molecule. Alternatively, the **antisense** molecule is a synthetic oligonucleotide. **Antisense** oligonucleotides will generally be at least about 7, usually at least about 12, more usually at least about 20 nucleotides. . .

SUMM [0090] A specific region or regions of the endogenous sense strand mRNA sequence is chosen to be complemented by the **antisense** sequence. Selection of a specific sequence for the oligonucleotide may use an empirical method, where several candidate sequences are assayed. . . animal model. A combination of sequences may also be used, where several regions of the mRNA sequence are selected for **antisense** complementation.

SUMM [0091] **Antisense** oligonucleotides may be chemically synthesized by methods known in the art (see Wagner et al. (1993) supra. and Milligan et. . .

SUMM [0093] As an alternative to **antisense** inhibitors, catalytic nucleic acid compounds, e.g. ribozymes, **antisense** conjugates,

etc. may be used to inhibit gene expression. Ribozymes may be synthesized in vitro and administered to the patient, or may be encoded on an expression vector, from which the **ribozyme** is synthesized in the targeted cell (for example, see International patent application WO 95/23225, and Beigelman et al. (1995) Nucl. Acids Res 23:4434-42). Examples of oligonucleotides with catalytic activity are described in WO 95/06764. Conjugates of **antisense** ODN with a metal complex, e.g. terpyridyl Cu(II), capable of mediating mRNA hydrolysis are described in Bashkin et al. (1995). . .

CLM What is claimed is:

8. The method according to claim 7, wherein said method comprises introducing **antisense** sequences specific for SEQ ID NO:1.

L14 ANSWER 15 OF 70 USPATFULL

ACCESSION NUMBER:	2002:191154 USPATFULL
TITLE:	Diagnostic/therapeutic agents
INVENTOR(S):	Klaveness, Jo, Oslo, NORWAY Rongved, Pal, Oslo, NORWAY Hogset, Anders, Oslo, NORWAY Tolleshaug, Helge, Oslo, NORWAY Cuthbertson, Alan, Oslo, NORWAY Godal, Aslak, Oslo, NORWAY Hoff, Lars, Oslo, NORWAY Gogstad, Geir, Oslo, NORWAY Bryn, Klaus, Oslo, NORWAY Naevestad, Anne, Oslo, NORWAY Lovhaug, Dagfinn, Oslo, NORWAY Hellebust, Halldis, Oslo, NORWAY Solbakken, Magne, Oslo, NORWAY
PATENT ASSIGNEE(S):	Nycomed Imaging AS (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002102217	A1	20020801
APPLICATION INFO.:	US 2001-925715	A1	20010810 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1997-959206, filed on 28 Oct 1997, PATENTED		

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1996-22366	19961028
	GB 1996-22369	19961028
	GB 1997-2195	19970204
	GB 1997-8265	19970424
	GB 1997-11837	19970606
	GB 1997-11839	19970606
	US 1997-49263P	19970607 (60)
	US 1997-49264P	19970606 (60)
	US 1997-49266P	19970607 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Richard E. Fichter, BACON & THOMAS, PLLC, Fourth Floor, 625 Slaters Lane, Alexandria, VA, 22314-1176
NUMBER OF CLAIMS:	38
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	1 Drawing Page(s)
LINE COUNT:	5190

SUMM . . . membranes doped with lipopeptide structures comprising a poly-L-lysine or poly-D-lysine chain in combination with a targeting vector. Applied to gene therapy/**antisense** technologies with particular emphasis on receptor-mediated drug delivery the microbubble carrier is condensed with DNA or RNA via elecrostatic interaction. . .

SUMM . . . E-selectin D inflammation

SPARC	tumors, inflammation		M
snake venoms (RGD-containing)	tumors, inflammation		Q
Tissue inhibitor of metalloproteinases	tumors, inflammation	e g,, TIMP-2	U
thrombin	tumors, inflammation		H
thrombin-receptor- H activating tetradecapeptide	tumors, inflammation		
thymidine phosphorylase	tumors, inflammation		D
tumor growth factor	tumors, inflammation		ZA

SUMM . . . M. E., E. Pipili-Synethos, E. Sakkoula, D. Panagiotopoulos, N. Craniti, and J. M. Matsoukas. 1996. "Inhibition of TRAP-induced angiogenesis by the tripeptide Phe-Pro-Arg, a **thrombin-receptor**-derived peptide analogue". Letters in Peptide Science 3: 227-232.

I. Nguyen, M. 1997. "Angiogenic factors as tumor markers". Investigational New Drugs 15 (1): 29-37.

J.. . . Cell. Biol. 17: 4015-4023.

T. Zimrin, A. B., M. S. Pepper, G. A. McMahon, F. Nguyen, R. Montesano, and T. Maciag. 1996. "An **Antisense** Oligonucleotide to the Notch Ligand Jagged Enhances Fibroblast Growth Factor-induced Angiogenesis <in vitro>". J. Bid. Chem. 271 (Dec. 20): 32499-3502.

U. Albini, A., R.. . . of the angiogenic factors vascular endothelial cell growth factor, acidic and basic fibroblast growth factor, tumor growth factor beta-1, platelet-derived endothelial cell growth factor, **placenta** growth factor and pleiotrophin in human primary breast cancer and its relation to angiogenesis. Cancer Res. 57, 963-9.

ZB. Carmeliet, P., L. Moons,. . .

L14 ANSWER 16 OF 70 USPATFULL

ACCESSION NUMBER: 2002:165193 USPATFULL

TITLE: Nucleic acids, proteins, and antibodies

INVENTOR(S): Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002086822	A1	20020704	
APPLICATION INFO.:	US 2001-764886	A1	20010117	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-179065P	20000131	(60)
	US 2000-180628P	20000204	(60)
	US 2000-214886P	20000628	(60)
	US 2000-217487P	20000711	(60)
	US 2000-225758P	20000814	(60)
	US 2000-220963P	20000726	(60)
	US 2000-217496P	20000711	(60)
	US 2000-225447P	20000814	(60)
	US 2000-218290P	20000714	(60)
	US 2000-225757P	20000814	(60)
	US 2000-226868P	20000822	(60)

US 2000-216647P 20000707 (60)
US 2000-225267P 20000814 (60)
US 2000-216880P 20000707 (60)
US 2000-225270P 20000814 (60)
US 2000-251869P 20001208 (60)
US 2000-235834P 20000927 (60)
US 2000-234274P 20000921 (60)
US 2000-234223P 20000921 (60)
US 2000-228924P 20000830 (60)
US 2000-224518P 20000814 (60)
US 2000-236369P 20000929 (60)
US 2000-224519P 20000814 (60)
US 2000-220964P 20000726 (60)
US 2000-241809P 20001020 (60)
US 2000-249299P 20001117 (60)
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US 2000-251856P 20001208 (60)
US 2000-251868P 20001208 (60)
US 2000-229344P 20000901 (60)
US 2000-234997P 20000925 (60)
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US 2000-229287P 20000901 (60)
US 2000-229513P 20000905 (60)
US 2000-231413P 20000908 (60)
US 2000-229509P 20000905 (60)
US 2000-236367P 20000929 (60)
US 2000-237039P 20001002 (60)
US 2000-237038P 20001002 (60)
US 2000-236370P 20000929 (60)
US 2000-236802P 20001002 (60)
US 2000-237037P 20001002 (60)
US 2000-237040P 20001002 (60)
US 2000-240960P 20001020 (60)
US 2000-239935P 20001013 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
LINE COUNT: 20931
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . based on their homology levels and/or the ligands they recognize. For example, the interleukin-8 receptor, the angiotensin II receptor, the **thrombin receptor**, the endothelin receptors, the N-formyl peptide receptor and the C5a receptor all bind peptide ligands and share 20-40% amino acid. . .

SUMM . . . of this original 5' RACE procedure. Poly A+ or total RNA is reverse transcribed with Superscript II (Gibco/BRL) and an **antisense** or complementary primer specific to the cDNA sequence. The primer is removed from the reaction with a Microcon Concentrator (Amicon).. . . sites. This double-stranded cDNA is PCR amplified for 40 cycles with the same primers as well as a nested cDNA-specific **antisense** primer. The PCR products are size-separated on an ethidium bromide-agarose gel and the region of gel containing cDNA products the. . .

SUMM . . . An alternative to generating 5' or 3' cDNA from RNA is to use cDNA library double-stranded DNA. An asymmetric PCR-amplified **antisense** cDNA strand is synthesized with an **antisense** cDNA-specific primer and a plasmid-anchored primer. These primers are

removed and a symmetric PCR reaction is performed with a nested cDNA-specific **antisense** primer and the plasmid-anchored primer.

SUMM . . . T-Cell disease Uni-ZAP XR

H0100 Human Whole Six Week Old Embryo Human Whole Six Week Old Embryo Embryo Uni-ZAP XR

H0111 Human **Placenta**, subtracted **Placenta** **Placenta** Human pBluescript

H0123 Human Fetal Dura Mater Human Fetal Dura Mater Brain Uni-ZAP XR

H0135 Human Synovial Sarcoma Synovium Human Synovial Uni-ZAP XR

. . . Human Bone fraction I Cell Line Osteoblastoma MG63 cell line Uni-ZAP XR

H0294 Amniotic Cells - TNF induced **Placenta** Cell Line Amniotic Cells - TNF induced Uni-ZAP XR

H0305 D34 positive cells (Cord Blood) Blood CD34 Positive Cells Cord ZAP Express

H0316 HUMAN STOMACH. . . H. Epididiymus, cauda Epididiymus, cauda Human Uni-ZAP XR

H0551 Human Thymus Stromal Cells pCMV Sport 3.0 Human Thymus Stromal Cells

H0553 Human **Placenta** **Placenta** 3.0 Human pCMVSport

H0555 Rejected Kidney, lib 4 disease pCMVSport 3.0 Human Rejected Kidney Kidney

H0556 Activated T-cell (12 h)/ Cell. . . T-Cells Blood

SUMM . . . CD40 activated pSport1 cells monocyte dendritic cells

H0641 LPS activated derived dendritic pSport1 cells LPS activated monocyte derived dendritic cells

H0644 Human **Placenta** (re-excision) **Placenta** **Placenta** Human Uni-ZAP XR

H0646 Lung, Cancer (4005313A3): Invasive Poorly Differentiated Lung Adenocarcinoma, pSport1 Metastatic squamous cell lung carcinoma, poorly di

H0648 Ovary, Cancer:. . . treated), re-excision Uni-ZAP XR Macrophage (GM-CSF treated)

S0280 Human Adipose Tissue, re-excision Human Adipose Tissue Uni-ZAP XR

S0284 7TMCTT (Testis) Testis 7TMCTP (**Placenta**) PCRII

S0308 Spleen/normal Spleen normal pSport1

S0318 Human Normal Cartilage Fraction II Human Normal Cartilage pSport1

S0344 Macrophage-oxLDL; re-excision macrophage- blood

Cell. . . Human Uterus, pBluescript SK-

T0071 Human Bone Marrow pBluescript SK- normal Human Bone Marrow

L0021 Human adult (K. Okubo)

L0055 Human promyelocyte

L0142 Human **placenta** cDNA (TFujiwara) **placenta**

L0362 Stratagene ovarian cancer Bluescript SK- (#937219)

L0366 Stratagene schizo brain Bluescript SK- S11 schizophrenic brain S-11 frontal lobe

L0384 NCI_CGAP_Pr23 pBluescript SK- precursor 937230 prostate. . . cells brain

L0598 Morton Fetal Cochlea pBluescript SK- cochlea ear

L0599 Stratagene lung (#937210) pBluescript SK- lung

L0603 Stratagene **placenta** (#937225) **placenta**

L0629 NCI_CGAP_Me13 (skin primary) pBluescript SK- pCMV-SPORT4 metastatic melanoma to bowel bowel

L0638 NCI_CGAP_Brn35 pCMV-SPORT6 tumor, 5 pooled (see description) brain

L0641 NCI_CGAP_Co17. . . SUMM . . . tumor ovary pT7T3D (Pharmacia) with a modified polylinker

L0752 Soares_parathyroid_tumor_NbHPA parathyroid tumor parathyroid pT7T3D (Pharmacia) with a modified polylinker gland

L0754 Soares **placenta** Nb2HP **placenta** pT7T3D (Pharmacia) with a modified polylinker

L0756 Soares_multiple_sclerosis_2NbHMSP multiple sclerosis lesions pT7T3D (Pharmacia) with a modified polylinker V_TYPE

L0757 Soares_senescent_fibroblasts_MbHSF senescent fibroblast. . .

SUMM . . . foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through **antisense** DNA or RNA. **Antisense** techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance Lee et. . . 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991))

or to the mRNA itself (**antisense**--Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988)). Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while **antisense** RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the **antisense** RNA or DNA may be expressed in vivo to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design **antisense** or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions. Non-limiting **antisense** and triple helix methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the section labeled "**Antisense** and **Ribozyme** (Antagonists)").

SUMM . . . into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., **antisense** or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and. . .

SUMM . . . or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and **antisense** DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires. . .

SUMM [0548] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, **antisense** nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example. . .

SUMM . . . telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo **implantation** controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter. . .

SUMM [0651] In one aspect of the birth control method, an amount of the compound sufficient to block embryo **implantation** is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a. . . and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal **implantation** in the treatment of endometriosis.

SUMM . . . abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, **placenta** previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the. . .

SUMM . . . into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., **antisense** or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and. . .

SUMM [0767] **Antisense** and **Ribozyme** (Antagonists)

SUMM . . . thereof, and/or to cDNA sequences contained in cDNA Clone ID NO:Z identified for example, in Table 1A. In one embodiment, **antisense** sequence is generated internally, by the organism, in another embodiment, the **antisense** sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). **Antisense** technology can be used to control gene expression through **antisense** DNA or RNA, or through triple-helix formation. **Antisense** techniques are discussed for example, in Okano, J.,

Neurochem. 56:560 (1991); Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance, Lee et. . .

SUMM [0769] For example, the use of c-myc and c-myb **antisense** RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described.. . . A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given **antisense** RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked. . .

SUMM . . . 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an **antisense** RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The **antisense** RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

SUMM [0771] In one embodiment, the **antisense** nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an **antisense** nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the **antisense** nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired **antisense** RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral,. . .

SUMM [0772] The **antisense** nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a. . . sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded **antisense** nucleic acids, a single strand of the duplex DNA may thus be tested, or **triplex** formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the **antisense** nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or **triplex** as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of. . .

SUMM . . . oligonucleotides complementary to either the 5'- or 3'-non-translated, non-coding regions of polynucleotide sequences described herein could be used in an **antisense** approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. **Antisense** oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, **antisense** nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50. . .

SUMM [0775] The **antisense** oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to,. . .

SUMM [0776] The **antisense** oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose,. . .

SUMM [0777] In yet another embodiment, the **antisense** oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a. . .

SUMM [0778] In yet another embodiment, the **antisense** oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with

complementary RNA in which, contrary to the. . .

SUMM [0780] While **antisense** nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

SUMM [0781] Potential antagonists according to the invention also include catalytic RNA, or a **ribozyme** (See, e.g., PCT International Publication WO 90/11364, published Oct. 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that. . . in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead **ribozyme** cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the **ribozyme** is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase. . .

SUMM [0782] As in the **antisense** approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g., for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the **ribozyme** may be introduced into the cell in the same manner as described above for the introduction of **antisense** encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the **ribozyme** under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the **ribozyme** to destroy endogenous messages and inhibit translation. Since ribozymes unlike **antisense** molecules, are catalytic, a lower intracellular concentration is required for efficiency.

SUMM . . . throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an **antisense** molecule directed to the polynucleotide of the present invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention.

DETD . . . that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, **antisense**.

DETD . . . HGBI
HLHA HLHB HLHC HLHD HLHE Human Fetal Lung III
Uni-ZAP XR LP03
HLHF HLHG HLHH HLHQ
HPMA HPMB HPMC HPMD HPME Human **Placenta**
Uni-ZAP XR LP03
HPMF HPMG HPMH
HPRA HPRB HPRC HPRD Human Prostate
Uni-ZAP XR LP03
HSIA HSIC HSID HSIE Human Adult Small Intestine. . .
DETD . . . Human endometrial stromal cells- pCMVSport3.0
LP08
treated with estradiol
HSYA HSYB HSYC Human Thymus Stromal Cells
pCMVSport3.0 LP08
HLWA HLWB HLWC Human **Placenta**
pCMVSport3.0 LP08
HRAA HRAB HRAC Rejected Kidney, lib 4
pCMVSport3.0 LP08
HMTM PCR, pBMC I/C treated
PCRII LP09
HMJA H. Meniingima, M6
pSport. . .
DETD . . . LP020
HTNT Tongue Tumour
pSport 1 LP020
HLXN Larynx Normal
pSport 1 LP020
HLXT Larynx Tumour
pSport 1 LP020
HTYN Thymus

	pSport 1	LP020	
HPLN			**Placenta**
	pSport 1	LP020	
HTNG			Tongue Normal
	pSport 1	LP020	
HZAA			Thyroid Normal (SDCA2 No)
	pSport 1	LP020	
HWES			Thyroid Thyroiditis
	pSport 1	LP020	

HFHD. . .

DETD . . . and which may be administered in combination with the compositons of the invention include, but are not lmited to, Angiozyme (**Ribozyme**, Boulder, Colo.), Anti-VEGF antibody (Genentech, S. San Francisco, Calif.), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, Calif.), SU-5416. . .

DETD [1037] In one example, **antisense** technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a. . .

DETD [1038] For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously **antisense** polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The **antisense** polynucleotides of the present invention can be formulated using techniques and formulations described herein (e.g. see Example 13), or otherwise. . .

DETD . . . treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and **antisense** DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the. . .

L14 ANSWER 17 OF 70 USPATFULL

ACCESSION NUMBER: 2002:157081 USPATFULL

TITLE: Compositions and methods for the therapy and diagnosis of prostate cancer

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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002081680	A1	20020627
APPLICATION INFO.:	US 2001-822827	A1	20010328 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-780669, filed on 9 Feb 2001, PENDING Continuation-in-part of Ser. No. US 2000-679272, filed on 4 Oct 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-157455P	20000417 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092	
NUMBER OF CLAIMS:	14	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	10 Drawing Page(s)	
LINE COUNT:	7692	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0746] As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or **antisense**) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which. . .

DETD [0777] According to another embodiment of the present invention, polynucleotide compositions comprising **antisense** oligonucleotides are provided. **Antisense** oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by. . . which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of **antisense** oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by **antisense** oligonucleotides directed to their respective mRNA sequences (U.S. Pat. Nos. 5,739,119 and 5,759,829). Further, examples of **antisense** inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABAA. . . Peris et al., Brain Res Mol Brain Res. Jun. 15, 1998; 57(2):310-20; U.S. Pat. Nos. 5,801,154; 5,789,573; 5,718,709 and 5,610,288). **Antisense** constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, e.g.. . .

DETD . . . sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the **antisense** oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment,. . . more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of **antisense** compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T.sub.m, binding energy, and relative stability. **Antisense** compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce. . .

DETD [0779] The use of an **antisense** delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic. . . al., Nucleic Acids Res. Jul. 15, 1997;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the **antisense** oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further,. . .

DETD . . . According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of **ribozyme** molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein. . . attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the **ribozyme** prior to chemical reaction.

DETD [0782] The enzymatic nature of a **ribozyme** is advantageous over

many technologies, such as **antisense** technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of **ribozyme** necessary to affect a therapeutic treatment is lower than that of an **antisense** oligonucleotide. This advantage reflects the ability of the **ribozyme** to act enzymatically. Thus, a single **ribozyme** molecule is able to cleave many molecules of target RNA. In addition, the **ribozyme** is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding. . . of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a **ribozyme**. Similar mismatches in **antisense** molecules do not prevent their action (Woolf et al., Proc Natl Acad Sci USA. Aug. 15, 1992;89(16):7305-9). Thus, the specificity of action of a **ribozyme** is greater than that of an **antisense** oligonucleotide binding the same RNA site.

DETD . . . an example of the RNaseP motif is described by Guerrier-Takada et al., Cell. December 1983;35(3 Pt 2):849-57; Neurospora VS RNA **ribozyme** motif is described by Collins (Saville and Collins, Cell. May 18, 1990;61(4):685-96; Saville and Collins, Proc Natl Acad Sci USA.. . . nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the **ribozyme** constructs need not be limited to specific motifs mentioned herein.

DETD [0785] **Ribozyme** activity can be optimized by altering the length of the **ribozyme** binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see e.g., Int. Pat. Appl.. . .

DETD . . . joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of **ribozyme** delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO. . .

DETD [0787] Another means of accumulating high concentrations of a **ribozyme**(s) within cells is to incorporate the **ribozyme** -encoding sequences into a DNA expression vector. Transcription of the **ribozyme** sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA. . .

DETD . . . are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, **Antisense** Nucleic Acid Drug Dev. 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have. . .

DETD [0793] Methods of characterizing the **antisense** binding properties of PNAs are discussed in Rose (Anal Chem. Dec. 15, 1993;65(24):3545-9) and Jensen et al. (Biochemistry. Apr. 22,. . .

DETD . . . of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, **antisense** inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome. . .

DETD . . . WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of **implantation**, the rate and expected duration of release and the nature of the condition to be treated or prevented.

DETD . . . subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, **placenta**, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This. . .

DETD [0982] P703P was found to show some homology to previously identified proteases, such as thrombin. The **thrombin receptor** has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of **thrombin receptor antisense** cDNA has

been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against **thrombin receptor** inhibit **thrombin receptor** activation and thrombin-induced platelet activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P. . .

DETD . . . and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an **antisense** cloning primer that contains an EcoRI site. DNA amplification was performed using 5 .mu.l 10X Pfu buffer, 1 .mu.l 20. . .

DETD . . . to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an **antisense** cloning primer that contains an EcoRI site and a stop codon. DNA amplification was performed essentially as described above. The. . .

DETD . . . and AW053 (SEQ ID NO: 850). AW042 is a sense cloning primer that contains a EcoRI site. AW053 is an **antisense** primer with stop and Xho I sites. DNA amplification was performed essentially as described above. The resulting PCR product was. . .

DETD . . . AW081 (SEQ ID NO: 815 and 816). AW080 is a sense cloning primer with an NdeI site. AW081 is an **antisense** cloning primer with a XhoI site. The PCR-amplified P788P, as well as the vector pCRX1, were digested with NdeI and. . .

DETD . . . (SEQ ID NO: 820 and 821, respectively). AW056 is a sense cloning primer with an EcoRI site. AW057 is an **antisense** primer with stop and XhoI sites. The amplified P501S fragment and Ra12/pCRX1 were digested with EcoRI and XhoI and then. . .

DETD . . . was used. The primer of SEQ ID NO: 828 created a 5' NcoI site and added a start codon. The **antisense** primer of SEQ ID NO: 829 creates a XhoI site on P510S C terminal fragment. Clones were confirmed by sequencing.. . .

DETD . . . primer with an NdeI site for use in ligating into pPDM. The primer of SEQ ID NO: 831 is an **antisense** primer with an added XhoI site for use in ligating into pPDM. The resulting fragment was cloned to pPDM at. . .

DETD . . . as follows: TCR Valpha-6 5' (sense): GGATCC---GCCGCCACC--ATGTCACTTTCTAGCCTGCT (SEQ ID NO: 899) BamHI site Kozak TCR alpha sequence TCR alpha 3' (**antisense**): GTCGAC---TCAGCTGGACCACAGCCGCAG (SEQ ID NO: 900) SalI site TCR alpha constant sequence TCR Vbeta-7. 5' (sense): GGATCC---GCCGCCACC--ATGGGCTGCAGGCTGCTCT (SEQ ID NO: 901) BamHI site Kozak TCR alpha sequence TCR beta 3' (**antisense**): GTCGAC---TCAGAAATCCTTTCTCTTGAC (SEQ ID NO: 902) SalI site TCR beta constant sequence. Standard 35 cycle RT-PCR reactions were established using cDNA. . .

L14 ANSWER 18 OF 70 USPATFULL

ACCESSION NUMBER: 2002:149131 USPATFULL

TITLE: 28 human secreted proteins

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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002077287	A1	20020620

APPLICATION INFO.: US 2001-852659 A1 20010511 (9)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-152060, filed on 11 Sep 1998, UNKNOWN
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 17779
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0038] This gene is expressed primarily in **placenta**, and to a lesser extent, in T-cells.

SUMM . . . this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g.immune, hematopoietic, **placenta**, and T-cells, and cancerous and wounded tissues) or bodily fluids (e.g.lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal. . .

SUMM [0118] The translation product of this gene shares sequence homology with a frog **thrombin receptor** [Xenopus laevis]. Moreover, another group recently cloned this same gene, also recognizing the homology to thrombing receptors. (See Accession NO:. . .

SUMM . . . effects. Additionally, neovascularization and various cell-type specific proliferation effects have been seen. The fact that this clone was isolated from **placenta** RNA may make this an interesting gene to characterize. The known neurokinins are expressed in either the central nervous system. . .

SUMM [0135] This gene is expressed primarily in human **placenta** and to a lesser extent in soares **placenta**.

SUMM . . . of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., **placenta**, and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine,. . .

SUMM [0192] This gene is expressed primarily in the testes and to a lesser extent in the lung, tonsils, **placenta**, and rhabdomyosarcoma.

SUMM . . . for diagnosis of diseases and conditions which include, but are not limited to, diseases related to the testes, lung, tonsils, **placenta**, and tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of. . . a number of disorders of the above tissues or cells, particularly of the diseases related to the testes, lung, tonsils, **placenta**, and tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., testes and other reproductive tissue, lung, tonsils, **placenta**, and striated muscle, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, serum, plasma, unne, synovial fluid or. . .

SUMM . . . and polypeptides corresponding to the gene are useful for diagnosis and treatment of diseases related to the testes, lung, tonsils, **placenta**, and tumors. More specifically, the tissue distribution indicates that the protein product of this clone is useful for the treatment. . .

SUMM [0209] This gene is expressed primarily in **placenta** and human amygdala, and to a lesser extent in adult brain, primary dendritic cells, keratinocytes, activated monocytes, human cerebellum, and. . .

SUMM . . . of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., **placenta**, amygdala, brain and other tissue of the nervous system, dendritic cells, blood cells, keratinocytes, and cancerous and wounded tissues) or. . .

SUMM [0467] In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or **antisense** DNA or RNA. **Antisense** techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991);

"Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRCPress, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance Lee et al.,. . . 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (**antisense**--Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while **antisense** RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design **antisense** or triple helix polynucleotides in an effort to treat or prevent disease.

SUMM . . . treatingor preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and **antisense** DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires. . .

SUMM [0598] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, **antisense** nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example. . .

SUMM . . . telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo **implantation** controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter. . .

SUMM [0702] In one aspect of the birth control method, an amount of the compound sufficient to block embryo **implantation** is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a. . . and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal **implantation** in the treatment of endometriosis.

SUMM . . . abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, **placenta** previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the. . .

SUMM . . . into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., **antisense** or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and. . .

SUMM [0842] **Antisense** And **Ribozyme** (Antagonists)

SUMM . . . in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, **antisense** sequence is generated internally by the organism, in another embodiment, the **antisense** sequence is separately administered (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Anitsense Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). **Antisense** technology can be used to control gene expression through **antisense** DNA or RNA, or through triple-helix formation. **Antisense** techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance, Lee et. . .

SUMM [0844] For example, the use of c-myc and c-myb **antisense** RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described.. . . A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given **antisense** RNA is

produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked. . .

SUMM . . . coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an **antisense** RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The **antisense** RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

SUMM [0846] In one embodiment, the **antisense** nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an **antisense** nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the **antisense** nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired **antisense** RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral,. . .

SUMM [0847] The **antisense** nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a. . . sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded **antisense** nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or **triplex** formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the **antisense** nucleic acid Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or **triplex** as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of. . .

SUMM . . . to either the 5'- or 3'-non-translated, non-coding regions of a polynucleotide sequence of the invention could be used in an **antisense** approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. **Antisense** oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA, **antisense** nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50. . .

SUMM [0850] The **antisense** oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to,. . .

SUMM [0851] The **antisense** oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose,. . .

SUMM [0852] In yet another embodiment, the **antisense** oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a. . .

SUMM [0853] In yet another embodiment, the **antisense** oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the. . .

SUMM [0855] While **antisense** nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated region. . .

SUMM [0856] Potential antagonists according to the invention also include catalytic RNA, or a **ribozyme** (See, e.g., PCT International Publication WO 90/11364, published Oct. 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While ribozymes that. . . in the art and is

described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead **ribozyme** cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the **ribozyme** is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the. . .

SUMM [0857] As in the **antisense** approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the **ribozyme** may be introduced into the cell in the same manner as described above for the introduction of **antisense** encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the **ribozyme** under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the **ribozyme** to destroy endogenous messages and inhibit translation. Since ribozymes unlike **antisense** molecules, are catalytic, a lower intracellular concentration is required for efficiency.

SUMM . . . throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an **antisense** molecule directed to the polynucleotide of the present invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention.

SUMM [0863] invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention.

DETD . . . such that in one orientation, single stranded rescue initiated-from the f1 ori generates sense strand DNA and in the other, **antisense**.

DETD . . . and which may be administered in combination with the compositons of the invention include, but are not lmited to, Angiozyme (**Ribozyme**, Boulder, Colo.), Anti-VEGF antibody (Genentech, S. San Francisco, Calif.), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, Calif.), SU-5416. . .

DETD [1150] In one example, **antisense** technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a. . . of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously **antisense** polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the **antisense** polynucleotide is provided in Example 23.

DETD . . . treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and **antisense** DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the. . .

L14 ANSWER 19 OF 70 USPATFULL
ACCESSION NUMBER: 2002:148614 USPATFULL
TITLE: 28 human secreted proteins
INVENTOR(S): Ruben, Steven M., Olney, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
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Wei, Ying-Fei, Berkeley, CA, UNITED STATES
Moore, Paul A., Germantown, MD, UNITED STATES
Young, Paul E., Gaithersburg, MD, UNITED STATES

Greene, John M., Gaithersburg, MD, UNITED STATES
Ferrie, Ann M., Painted Post, NY, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002076756	A1	20020620	
APPLICATION INFO.:	US 2001-853161	A1	20010511	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-265583P	20010202	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 17788
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0037] This gene is expressed primarily in **placenta**, and to a lesser extent, in T-cells.

SUMM . . . this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g.immune, hematopoietic, **placenta**, and T-cells, and cancerous and wounded tissues) or bodily fluids (e.g.lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal. . .

SUMM [0107] The translation product of this gene shares sequence homology with a frog **thrombin receptor** [Xenopus laevis]. Moreover, another group recently cloned this same gene, also recognizing the homology to thrombing receptors. (See Accession NO:. . .

SUMM . . . effects. Additionally, neovascularization and various cell-type specific proliferation effects have been seen. The fact that this clone was isolated from **placenta** RNA may make this an interesting gene to characterize. The known neurokinins are expressed in either the central nervous system. . .

SUMM [0121] This gene is expressed primarily in human **placenta** and to a lesser extent in soares **placenta**.

SUMM . . . of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., **placenta**, and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine,. . .

SUMM [0171] This gene is expressed primarily in the testes and to a lesser extent in the lung, tonsils, **placenta**, and rhabdomyosarcoma.

SUMM . . . for diagnosis of diseases and conditions which include, but are not limited to, diseases related to the testes, lung, tonsils, **placenta**, and tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of. . . a number of disorders of the above tissues or cells, particularly of the diseases related to the testes, lung, tonsils, **placenta**, and tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., testes and other reproductive tissue, lung, tonsils, **placenta**, and striated muscle, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, serum, plasma, urine, synovial fluid or. . .

SUMM . . . and polypeptides corresponding to the gene are useful for diagnosis and treatment of diseases related to the testes, lung, tonsils, **placenta**, and tumors. More specifically, the tissue distribution indicates that the protein product of this clone is useful for the treatment. . .

SUMM [0188] This gene is expressed primarily in **placenta** and human amygdala, and to a lesser extent in adult brain, primary dendritic cells, keratinocytes, activated monocytes, human cerebellum, and. . .

SUMM . . . of this gene at significantly higher or lower levels may be

routinely detected in certain tissues or cell types (e.g., **placenta**, amygdala, brain and other tissue of the nervous system, dendritic cells, blood cells, keratinocytes, and cancerous and wounded tissues) or. . .

SUMM [0452] In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or **antisense** DNA or RNA. **Antisense** techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRCPress, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance Lee et al.,. . . (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (**antisense**--Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while **antisense** RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design **antisense** or triple helix polynucleotides in an effort to treat or prevent disease.

SUMM . . . or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and **antisense** DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires. . .

SUMM [0585] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, **antisense** nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example. . .

SUMM . . . telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo **implantation** controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter. . .

SUMM [0688] In one aspect of the birth control method, an amount of the compound sufficient to block embryo **implantation** is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a. . . and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal **implantation** in the treatment of endometriosis.

SUMM . . . abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, **placenta** previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the. . .

SUMM . . . into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., **antisense** or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and. . .

SUMM [0829] **Antisense** and **Ribozyme** (Antagonists)

SUMM . . . in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, **antisense** sequence is generated internally by the organism, in another embodiment, the **antisense** sequence is separately administered (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Anitsense Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). **Antisense** technology can be used to control gene expression through **antisense** DNA or RNA, or through triple-helix formation. **Antisense** techniques are discussed for example, in Okano, Neurochem., 56:560 (1991);

Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance, Lee et. . .

SUMM [0831] For example, the use of c-myc and c-myb **antisense** RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described.. . . A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given **antisense** RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked. . .

SUMM . . . coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an **antisense** RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The **antisense** RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

SUMM [0833] In one embodiment, the **antisense** nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an **antisense** nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the **antisense** nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired **antisense** RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral,. . .

SUMM [0834] The **antisense** nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a. . . sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded **antisense** nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or **triplex** formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the **antisense** nucleic acid Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or **triplex** as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of. . .

SUMM . . . to either the 5'- or 3'-non-related, non-coding regions of a polynucleotide sequence of the invention could be used in an **antisense** approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. **Antisense** oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA, **antisense** nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50. . .

SUMM [0837] The **antisense** oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to,. . .

SUMM [0838] The **antisense** oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose,. . .

SUMM [0839] In yet another embodiment, the **antisense** oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a. . .

SUMM [0840] In yet another embodiment, the **antisense** oligonucleotide is an a-anomeric oligonucleotide. An a-anomenrc oligonucleotide forms specific double-stranded hybrids with

complementary RNA in which, contrary to the. . .

SUMM [0842] While **antisense** nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated region. . .

SUMM [0843] Potential antagonists according to the invention also include catalytic RNA, or a **ribozyme** (See, e.g., PCT International Publication WO 90/11364, published Oct. 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While ribozymes that. . . in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead **ribozyme** cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the **ribozyme** is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the. . .

SUMM [0844] As in the **antisense** approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the **ribozyme** may be introduced into the cell in the same manner as described above for the introduction of **antisense** encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the **ribozyme** under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the **ribozyme** to destroy endogenous messages and inhibit translation. Since ribozymes unlike **antisense** molecules, are catalytic, a lower intracellular concentration is required for efficiency.

SUMM . . . throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an **antisense** molecule directed to the polynucleotide of the present invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention. invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention.

DETD . . . that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, **antisense**.

DETD . . . and which may be administered in combination with the compositons of the invention include, but are not limited to, Angiozyme (**Ribozyme**, Boulder, Colo.), Anti-VEGF antibody (Genentech, S. San Francisco, Calif.), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, Calif.), SU-5416. . .

DETD [1165] In one example, **antisense** technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a. . . of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously **antisense** polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the **antisense** polynucleotide is provided in Example 23.

DETD . . . treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and **antisense** DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the. . .

L14 ANSWER 20 OF 70 USPATFULL

ACCESSION NUMBER: 2002:148613 USPATFULL

TITLE: G protein coupled receptor (GPCR) agonists and antagonists and methods of activating and inhibiting GPCR using the same

INVENTOR(S): Kuliopulos, Athan, Winchester, MA, UNITED STATES
Covic, Lidija, Boston, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002076755	A1	20020620	
APPLICATION INFO.:	US 2001-841091	A1	20010423	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-198993P	20000421 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Ivor R. Elrifi, Esq., MINTZ, LEVIN, COHN, FERRIS,, GLOVSKY and POPEO, P.C., One Financial Center, Boston, MA, 02111
NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 20 Drawing Page(s)
LINE COUNT: 1904
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and/or antagonists for their own receptors. Lipidated extracellular loop peptides were found to be full antagonists of extracellular ligands for **PAR 1**. Therefore, these novel molecular reagents will be applicable to a broad range of both known and unknown GPCRs.

DETD . . . digestive tract, blood vessel, heart, thymus, spleen, submandibular gland, peripheral blood, peripheral blood leukocyte, intestinal tract, prostate, testicle, testis, ovarium, **placenta**, uterus, bone, joint, small intestine, large intestine, skeletal muscle and the like, in particular, brain and various parts of the. . .

DETD . . . about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA that can include sense/**antisense** pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the. . .

DETD . . . black column. The extracellular agonists used to define maximum stimulation for each receptor (open column) were 10 nM thrombin for **PAR 1**, 100 micromolar SLIGKV for PAR2, 100 nM thrombin for PAR4, 300 nM CCK-8 for CCKA and CCKB, 1 micromolar AGCKNFFWKTFTSC. . .

DETD . . . Proc. Natl. Acad. Sci. (USA) 95, 6642-6646 (1998); M. L. Kahn et al., Nature 394, 690-694 (1998)) is a second **thrombin receptor** that plays a unique role in platelet aggregation (L. Covic, A. L. Gresser, A. Kuliopulos, Biochemistry 39, 5458-5467 (2000)).

L14 ANSWER 21 OF 70 USPATFULL
ACCESSION NUMBER: 2002:105925 USPATFULL
TITLE: Method and product for regulating apoptosis
INVENTOR(S): Johnson, Gary L., Boulder, CO, UNITED STATES
PATENT ASSIGNEE(S): National Jewish Center for Immunology and Respiratory Medicine (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002055130	A1	20020509	
APPLICATION INFO.:	US 2001-858754	A1	20010516	(9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1998-23130, filed on 13 Feb 1998, ABANDONED			

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-39740P	19970214 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
NUMBER OF CLAIMS: 39

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Page(s)
LINE COUNT: 6845
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . growth factor (EGF) receptor) and receptors that are coupled to heterotrimeric guanine nucleotide binding proteins (G proteins) such as the **thrombin receptor**. In addition, receptors like the T cell (TCR) and B cell (BCR) receptors are non-covalently associated with src family tyrosine. . .

DETD . . . per molecule; (ii) denaturing the double stranded DNA; (iii) renaturing the DNA to form double stranded DNA which can include sense/**antisense** pairs from different nicked products; (iv) removing single stranded portions from reformed duplexes by treatment with SI nuclease; and (v). . .

DETD . . . of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single (sense or **antisense**) and double-stranded polynucleotides.

DETD . . . for example, expression of MEKK proteins by cells. Such therapeutic applications include the use of such oligonucleotides in, for example, **antisense**-, **triplex** formation-, **ribozyme**- and/or RNA drug-based technologies. The present invention, therefore, includes use of such oligonucleotides and methods to interfere with the production. . .

DETD [0119] To further illustrate, another aspect of the invention relates to the use of the isolated nucleic acid in "**antisense**" therapy. As used herein, "**antisense**" therapy refers to administration or in situ generation of oligonucleotide probes or their derivatives which specifically hybridize (e.g. bind) under. . . the case of binding to DNA duplexes, through specific interactions in the major groove of the double helix. In general, "**antisense**" therapy refers to the range of techniques generally employed in the art, and includes any therapy which relies on specific. . .

DETD [0120] An **antisense** construct of the present invention can be delivered, for example, as an expression plasmid which, when transcribed in the cell,. . . is complementary to at least a unique portion of the cellular mRNA which encodes a vertebrate MEKK protein. Alternatively, the **antisense** construct is an oligonucleotide probe which is generated ex vivo and which, when introduced into the cell causes inhibition of. . . to endogenous nucleases, e.g. exonucleases and/or endonucleases, and are therefore stable in vivo. Exemplary nucleic acid molecules for use as **antisense** oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Pat. Nos. 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in **antisense** therapy have been reviewed, for example, by Van der Krol et al. (1988) Biotechniques 6:958-976; and Stein et al. (1988). . .

DETD . . . are useful in therapeutic, diagnostic, and research contexts. In therapeutic applications, the oligomers are utilized in a manner appropriate for **antisense** therapy in general. For such therapy, the oligomers of the invention can be formulated for a variety of loads of. . .

DETD [0124] Likewise, the **antisense** constructs of the present invention, by antagonizing the normal biological activity of one of the MEKK proteins, can be used. . .

DETD [0125] Furthermore, the anti-sense techniques (e.g. microinjection of **antisense** molecules, or transfection with plasmids whose transcripts are anti-sense with regard to a MEKK mRNA or gene sequence) can be. . .

DETD . . . by a MEKK-dependent pathway, can be, as appropriate, any of the preparations described above, including isolated polypeptides, gene therapy constructs, **antisense** molecules, peptidomimetics or agents identified in the drug assays provided herein.

DETD . . . can be utilized in conjunction with transplantation of such artificial livers, as well as embryonic liver structures, to promote

intraperitoneal **implantation**, vascularization, and in vivo differentiation and maintenance of the engrafted liver tissue.

DETD . . . similar fashion, the subject method can be applied to enhancing both the generation of prosthetic cartilage devices and to their **implantation**. In one embodiment of the subject method, the implants are contacted with a MEKK therapeutic during the culturing process so. . .

DETD . . . subject method is used to enhance attachment of prosthetic devices. To illustrate, the subject method can be used in the **implantation** of a periodontal prosthesis, wherein the treatment of the surrounding connective tissue stimulates formation of periodontal ligament about the prosthesis,. . .

DETD . . . encode the wild-type form of the protein, or can encode homologs thereof, including both agonists and antagonists, as well as **antisense** constructs. In preferred embodiments, the expression of the transgene is restricted to specific subsets of cells, tissues or developmental stages. . .

DETD . . . which interferes with the expression of a recombinant MEKK gene, such as one which encodes an antagonistic homolog or an **antisense** transcript, can be designed to activate expression of that gene. This interference with expression of the protein can result from. . .

DETD . . . A third type of target cell for transgene introduction is the embryonic stem cell (ES). ES cells are obtained from pre-**implantation** embryos cultured in vitro and fused with embryos (Evans et al. (1981) Nature 292:154-156; Bradley et al. (1984) Nature 309:255-258;. . .

L14 ANSWER 22 OF 70 USPATFULL

ACCESSION NUMBER: 2002:99081 USPATFULL

TITLE: Compositions and methods for the therapy and diagnosis of prostate cancer

INVENTOR(S): Xu, Jiangchun, Bellevue, WA, UNITED STATES
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McNeill, Patricia D., Des Moines, WA, UNITED STATES
Houghton, Raymond L., Bothell, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002051977	A1	20020502
APPLICATION INFO.:	US 2001-780669	A1	20010209 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-759143, filed on 12 Jan 2001, PENDING Continuation-in-part of Ser. No. US 2000-709729, filed on 9 Nov 2000, PENDING Continuation-in-part of Ser. No. US 2000-685166, filed on 10 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-679426, filed on 2 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-657279, filed on 6 Sep 2000, PENDING Continuation-in-part of Ser. No.

US 2000-651236, filed on 29 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-636215, filed on 10 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-605783, filed on 27 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-593793, filed on 13 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-510737, filed on 1 May 2000, GRANTED, Pat. No. US 6219981 Continuation-in-part of Ser. No. US 2000-568100, filed on 9 May 2000, PENDING Continuation-in-part of Ser. No. US 2000-536857, filed on 27 Mar 2000, PENDING Continuation-in-part of Ser. No. US 2000-483672, filed on 14 Jan 2000, PENDING Continuation-in-part of Ser. No. US 1999-443686, filed on 18 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-439313, filed on 12 Nov 1999, PENDING Continuation-in-part of Ser. No. US 1999-352616, filed on 13 Jul 1999, PENDING Continuation-in-part of Ser. No. US 1999-288946, filed on 9 Apr 1999, PENDING Continuation-in-part of Ser. No. US 1999-232149, filed on 15 Jan 1999, PENDING Continuation-in-part of Ser. No. US 1998-159812, filed on 23 Sep 1998, PENDING Continuation-in-part of Ser. No. US 1998-115453, filed on 14 Jul 1998, PENDING Continuation-in-part of Ser. No. US 1998-30607, filed on 25 Feb 1998, GRANTED, Pat. No. US 6262245 Continuation-in-part of Ser. No. US 1998-20956, filed on 9 Feb 1998, GRANTED, Pat. No. US 6261562 Continuation-in-part of Ser. No. US 1997-904804, filed on 1 Aug 1997, ABANDONED Continuation-in-part of Ser. No. US 1997-806099, filed on 25 Feb 1997, ABANDONED Continuation-in-part of Ser. No. WO 1998-US3492, filed on 25 Feb 1998, UNKNOWN Continuation-in-part of Ser. No. WO 1999-US15838, filed on 14 Jul 1999, UNKNOWN

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 7556
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0720] As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or **antisense**) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HNRNA molecules, which. . .

DETD [0751] According to another embodiment of the present invention, polynucleotide compositions comprising **antisense** oligonucleotides are provided. **Antisense** oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by. . . which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of **antisense** oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by **antisense** oligonucleotides directed to their respective mRNA sequences (U.S. Pat. No. 5,739,119 and U.S. Pat. No. 5,759,829). Further, examples of **antisense** inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA.sub.A. . . 1998 Jun 15;57(2):310-20; U.S. Pat. No. 5,801,154; U.S. Pat. No. 5,789,573; U.S. Pat. No. 5,718,709 and U.S. Pat. No. 5,610,288). **Antisense** constructs have also been described that inhibit and can be used to treat a variety

of abnormal cellular proliferations, e.g.. . .

DETD . . . sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the **antisense** oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment,. . . more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of **antisense** compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T.sub.m, binding energy, and relative stability. **Antisense** compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce. . .

DETD [0753] The use of an **antisense** delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic. . . al., Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the **antisense** oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further,. . .

DETD . . . According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of **ribozyme** molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein. . . attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the **ribozyme** prior to chemical reaction.

DETD [0756] The enzymatic nature of a **ribozyme** is advantageous over many technologies, such as **antisense** technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of **ribozyme** necessary to affect a therapeutic treatment is lower than that of an **antisense** oligonucleotide. This advantage reflects the ability of the **ribozyme** to act enzymatically. Thus, a single **ribozyme** molecule is able to cleave many molecules of target RNA. In addition, the **ribozyme** is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding. . . of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a **ribozyme**. Similar mismatches in **antisense** molecules do not prevent their action (Woolf et al., Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the specificity of action of a **ribozyme** is greater than that of an **antisense** oligonucleotide binding the same RNA site.

DETD . . . an example of the RNaseP motif is described by Guerrier-Takada et al., Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA **ribozyme** motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U. . . nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the **ribozyme** constructs need not be limited to specific motifs mentioned herein.

DETD [0759] **Ribozyme** activity can be optimized by altering the length of the **ribozyme** binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see e.g., Int. Pat. Appl.. . .

DETD . . . joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of **ribozyme** delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO. . .

DETD [0761] Another means of accumulating high concentrations of a

ribozyme(s) within cells is to incorporate the **ribozyme** -encoding sequences into a DNA expression vector. Transcription of the **ribozyme** sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA. . .

DETD . . . are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, **Antisense** Nucleic Acid Drug Dev. 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have. . .

DETD [0767] Methods of characterizing the **antisense** binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen et al. (Biochemistry. 1997 Apr. . .

DETD . . . of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, **antisense** inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome. . .

DETD . . . WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of **implantation**, the rate and expected duration of release and the nature of the condition to be treated or prevented.

DETD . . . subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, **placenta**, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This. . .

DETD [0959] P703P was found to show some homology to previously identified proteases, such as thrombin. The **thrombin receptor** has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of **thrombin receptor antisense** cDNA has been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against **thrombin receptor** inhibit **thrombin receptor** activation and thrombin-induced platelet activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P. . .

DETD . . . and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an **antisense** cloning primer that contains an EcoRI site. DNA amplification was performed using 5 .mu.l 10.times. Pfu buffer, 1 .mu.l 20. . .

DETD . . . to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an **antisense** cloning primer that contains an EcoRi site and a stop codon. DNA amplification was performed essentially as described above. The. . .

DETD . . . and AW053 (SEQ ID NO: 850). AW042 is a sense cloning primer that contains a EcoRi site. AW053 is an **antisense** primer with stop and Xho I sites. DNA amplification was performed essentially as described above. The resulting PCR product was. . .

DETD . . . AW081 (SEQ ID NO: 815 and 816). AW080 is a sense cloning primer with an NdeI site. AW081 is an **antisense** cloning primer with a XhoI site. The PCR-amplified P788P, as well as the vector pCRX1, were digested with NdeI and. . .

DETD . . . (SEQ ID NO: 820 and 821, respectively). AW056 is a sense cloning primer with an EcoRi site. AW057 is an **antisense** primer with stop and XhoI sites. The amplified P501S fragment and Ra12/pCRX1 were digested with EcoRI and XhoI and then. . .

DETD . . . was used. The primer of SEQ ID NO: 828 created a 5' NcoI site and added a start codon. The **antisense** primer of SEQ ID NO: 829 creates a XhoI site on P510S C terminal fragment. Clones were confirmed by sequencing.. . .

DETD . . . primer with an NdeI site for use in ligating into pPDM. The primer of SEQ ID NO: 831 is an **antisense** primer with an added XhoI site for use in ligating into pPDM. The resulting fragment was cloned to pPDM at. . .

DETD . . . were as follows: TCR Valpha-6 5'(sense): GGATCC--GCCGCCACC--

ATGTCACTTTCTAGCCTGCT (SEQ ID NO: 899) BamHI site Kozak TCR alpha sequence TCR alpha 3' (**antisense**): GTCGAC--TCAGCTGGACCACAGCCGCAG (SEQ ID NO: 900) Sa1I site TCR alpha constant sequence TCR Vbeta-7. 5'(sense): GGATCC--GCCGCCACC--ATGGGCTGCAGGCTGCTCT (SEQ ID NO: 901) BamHI site Kozak TCR alpha sequence TCR beta 3' (**antisense**): GTCGAC--TCAGAAATCCTTTCTCTTGAC (SEQ ID NO: 902) Sa1I site TCR beta constant sequence. Standard 35 cycle RT-PCR reactions were established using cDNA. . .

L14 ANSWER 23 OF 70 USPATFULL

ACCESSION NUMBER:	2002:92054 USPATFULL
TITLE:	Chimeric polypeptides of serum albumin and uses related thereto
INVENTOR(S):	Gyuris, Jeno, Winchester, MA, UNITED STATES Lamphere, Lou, Newton, MA, UNITED STATES Morris, Aaron, Brighton, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002048571	A1	20020425
APPLICATION INFO.:	US 2001-768183	A1	20010123 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-764918, filed on 18 Jan 2001, PENDING Continuation-in-part of Ser. No. US 2000-619285, filed on 19 Jul 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-144534P	19990719 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624
NUMBER OF CLAIMS:	53
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	16 Drawing Page(s)
LINE COUNT:	1937

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . transfecting cells either ex vivo or in vivo with genetic material encoding a chimeric polypeptide. Approaches include insertion of the **antisense** nucleic acid in viral vectors including recombinant retroviruses, adenoviruses, adeno-associated viruses, human immunodeficiency viruses, and herpes simplex viruses-1, or recombinant. . .

DETD . . . which part of the retroviral coding sequence (gag, pol, env) has been replaced by nucleic acid encoding one of the **antisense** E6AP constructs, rendering the retrovirus replication defective. The replication defective retrovirus is then packaged into virions which can be used. . .

DETD . . . of water, porosity and consequent permeability characteristics can be controlled. The selection of the shape, size, polymer, and method for **implantation** can be determined on an individual basis according to the disorder to be treated and the individual patient response. The. . .

DETD . . . substance K (neurokinin A) receptor, fMLP receptor, fMLP-like receptor, angiotensin II type 1 receptor, endothelin ETA receptor, endothelin ETB receptor, **thrombin receptor**, growth hormonereleasing hormone (GHRH) receptor, vasoactive intestinal peptide receptor, oxytocin receptor, somatostatin SSTR1 and SSTR2, SSTR3, cannabinoid receptor, follicle stimulating. . .

L14 ANSWER 24 OF 70 USPATFULL

ACCESSION NUMBER:	2002:85547 USPATFULL
TITLE:	Hirulog-like peptide and gene therapy
INVENTOR(S):	Shen, Gary, Winnipeg, CANADA

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002045589	A1	20020418	
APPLICATION INFO.:	US 2001-822882	A1	20010330	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-193114P	20000330 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KOHN & ASSOCIATES, 30500 Northwestern Highway, Suite 410, Farmington Hills, MI, 48334
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 2150
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0010] The **thrombin receptor** has a long extracellular extension, which contains a proposed cleavage site for the enzyme and a binding site for thrombin. The proteolytic cleavage of **thrombin receptor** generates a short peptide with a newly exposed NH2 terminus, known as "tethered ligand", which helps to activate the receptor. The **thrombin receptor** has seven hydrophobic segments spanning the lipid bilayer of plasma membrane and its intracellular extension is coupled with G protein. . .

SUMM [0011] Inhibitory G protein-coupled **thrombin receptor**, tyrosine kinase, phospholipase C and protein kinase C are involved in the regulation of thrombin-induced PAI-1 production in vascular SMC. . . responses related to cell growth and tissue remodeling via transmembrane signaling, which may be blocked by inhibitors targeted to the **thrombin receptor** or corresponding signaling pathway.

SUMM . . . patients with post-angioplasty restenosis (Ischinger T A, 1998; Ishiwata S et al, 1997, Tsakirirs D A et al, 1999). Stent **implantation** following angiography has virtually abolished periprocedural obstructive dissection and delays the occurrence of restenosis. The rates of intracoronary thrombosis and late restenosis were not reduced by stent **implantation**. Recurrent in-stent restenosis or vascular complications frequently occurred in the receivers. Stent-related vascular complications were found in some receivers. Extensive. . .

DETD . . . amino acids was identified. The present invention provides a HLP (32 amino acids) based on the structures of hirulog-1 and **thrombin receptor** (FPESKATNATLDPRPGGGGNGDFEEIPEEYLQ) (SEQ ID No: 1). Multiple prolonged intravenous infusions of HLP inhibited balloon catheter injury-induced stenosis by 30%-40%. Unlike hirulog-1,. . .

DETD . . . acquired disease or condition phenotype. The genetic material of interest encodes a product (e.g. a protein, polypeptide, peptide, functional RNA, **antisense**) whose production in vivo is desired. For example, the genetic material of interest can encode a hormone, receptor, enzyme, polypeptide. . .

DETD . . . leading sequence, hirulog2-9 [Maraganore J M et al. 1990 Biochemistry 29:7095-101] and hirudin54-65 [Forckamp E et al. 1986 DNA 5:511-7]. **Antisense** single-strand DNA encoding the prototype of HLP and sense single-strand DNA encoding hGH signal peptide is synthesized. Double-strand HLP-hGH DNA. . .

DETD . . . acid in hirulog-1 is replaced by a 12 amino acid leading sequence mimicking a portion of N-terminal domain of the **thrombin receptor**. This is designed to enhance the inhibitory effect of HLP on the binding of thrombin to its receptor. The presence. . .

DETD [0186] HLP (FPESKATNATLDPRPGGGGNGDFEEIPEEYLQ, Provisional Patent No. 60/193,114) was designed based on the sequences of hirulog-1 and the **thrombin receptor** (Clowes A W et al, 1991, Narins C R

et al 1998). Hirulog-1 was prepared as previously described (Clowes A.
. .

DETD . . . amino-terminal tail of HLP contains a region which is homology to a distal portion of the extracellular domain of the **thrombin receptor**. This region of HLP is structurally distinct from hirulog-19-20 (or HLP20-31) which aims the anion binding exosite of thrombin (Carmeliet P et al, 1997). HLP provides double-site of inhibition on the binding of thrombin to the **thrombin receptor**, which can more effectively reduce the activation of the thrombin inhibitor and the cellular effects of thrombin. In addition, the. . .

CLM What is claimed is:

. . . The hirulog-like peptide according to claim 1, wherein said hirulog-like peptide comprises a sequence based upon hirulog-1 and binds a **thrombin receptor**.

. . . The pharmaceutical composition according to claim 7, wherein said hirulog-like peptide consists of a sequence based upon hirulog-1 and a **thrombin receptor**.

L14 ANSWER 25 OF 70 USPATFULL

ACCESSION NUMBER: 2002:72993 USPATFULL
TITLE: Epstein barr virus induced genes
INVENTOR(S): Birkenbach, Mark, Tinley Park, IL, UNITED STATES
Kieff, Elliot, Brookline, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002040133	A1	20020404
APPLICATION INFO.:	US 2001-929583	A1	20010814 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-536954, filed on 28 Mar 2000, PENDING Division of Ser. No. US 1994-352678, filed on 30 Nov 1994, GRANTED, Pat. No. US 6043351 Continuation of Ser. No. US 1992-980518, filed on 25 Nov 1992, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOLF GREENFIELD & SACKS, PC, FEDERAL RESERVE PLAZA, 600 ATLANTIC AVENUE, BOSTON, MA, 02210-2211
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 2122
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . EBI 3 polypeptides; EBI 1, EBI 2, or EBI 3 polypeptides; recombinant DNA molecules; cells containing the recombinant DNA molecules; **antisense** EBI 1, EBI 2, or EBI 3 constructs; antibodies having binding affinity to an EBI 1, EBI 2, or EBI. . .

SUMM . . . EBI 3 polypeptides; EBI 1, EBI 2, or EBI 3 polypeptides; recombinant DNA molecules; cells containing the recombinant DNA molecules; **antisense** EBI 1, EBI 2, or EBI 3 constructs; antibodies having binding affinity to an EBI 1, EBI 2, or EBI. . .

DRWD . . . and immunoglobulin mu chain (IgU) probes were hybridized to RNA samples from the following human tissues: heart (HE), brain (BR), **placenta** (PL), lung (LU), liver (LI), kidney (KI), skeletal muscle (SM) and pancreas (PA). Numbers at the left indicate positions and. . .

DRWD . . . Tissue Northern, Clontech, Calif.) containing polyadenylated RNA (2 .mu.g/lane) from each of the following human tissues: heart (HE), brain BR), **placenta** (PL), lung (LU), liver (LI), kidney (KI), skeletal muscle (SM) and pancreas (PA). The EBI 3 probe specifically detects an. . .

DETD . . . peptide sequence in order to generate rationally designed antipeptide peptides, for example see Hurby et al., "Application of

Synthetic Peptides: **Antisense** Peptides", In Synthetic Peptides, A User's Guide, W. H. Freeman, NY, pp. 289-307 (1992), and Kaspczak et al., Biochemistry 28:9230-8. . .

DETD . . . examine gene expression in other human tissues, a commercially prepared blot was purchased containing 2 .mu.g of polyadenylated heart, brain, **placenta**, lung, liver, kidney, skeletal muscle and pancreas RNA (Multiple Tissue Northern, Clontech, Palo Alto, Calif.).

DETD . . . The EBI 2 gene does not have such a close homologue. EBI 2 has 24% amino acid identity to the **thrombin receptor** (Vu, T. K., et al., Cell 64(6):1057-68 (1991)). Less extensive homologies are observed with a number of other G-protein coupled. . .

DETD . . . EBI 3 RNA was also analyzed in a variety of non-lymphoid human tissues (FIG. 7A). Abundant expression was observed in **placenta**, significantly exceeding expression levels observed in any lymphoid cell type. EBI 3 RNA was also faintly detectable in liver RNA.. . .

L14 ANSWER 26 OF 70 USPATFULL

ACCESSION NUMBER: 2002:43170 USPATFULL

TITLE: Methods and reagents for isolating biologically active antibodies

INVENTOR(S): Gyuris, Jeno, Winchester, MA, UNITED STATES
Ewert, Sebastian-Meier, Wolfratshausen, GERMANY, FEDERAL REPUBLIC OF
Nagy, Zolton, Wolfratshausen, GERMANY, FEDERAL REPUBLIC OF
Morris, Aaron, Brighton, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002025536	A1	20020228	
APPLICATION INFO.:	US 2001-891557	A1	20010626	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-214200P	20000626 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624
NUMBER OF CLAIMS: 83
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 3051
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . example, angiogenesis is normally observed in wound healing, fetal and embryonal development, and formation of the corpus luteum, endometrium and **placenta**. The term "endothelium" means a thin layer of flat epithelial cells that lines serous cavities, lymph vessels, and blood vessels.. . .

DETD . . . beneficial gene. Repression may be achieved by operably linking a receptor- induced promoter to a gene encoding mRNA which is **antisense** to at least a portion of the mRNA encoded by the marker gene (whether in the coding or flanking regions),. . .

DETD . . . substance K (neurokinin A) receptor, fMLP receptor, fMLP-like receptor, angiotensin II type 1 receptor, endothelin ETA receptor, endothelin ETB receptor, **thrombin receptor**, growth hormone-releasing hormone (GHRH) receptor, vasoactive intestinal antibody receptor, oxytocin receptor, somatostatin SSTR1 and SSTR2, SSTR3, cannabinoid receptor, follicle stimulating. . .

L14 ANSWER 27 OF 70 USPATFULL

ACCESSION NUMBER: 2002:37531 USPATFULL

TITLE: Compositions and methods for the therapy and diagnosis of prostate cancer

INVENTOR(S): Xu, Jiangchun, Bellevue, WA, UNITED STATES

Dillon, Davin C., Issaquah, WA, UNITED STATES
Mitcham, Jennifer L., Redmond, WA, UNITED STATES
Harlocker, Susan L., Seattle, WA, UNITED STATES
Jiang, Yuqiu, Kent, WA, UNITED STATES
Kalos, Michael D., Seattle, WA, UNITED STATES
Fanger, Gary R., Mill Creek, WA, UNITED STATES
Retter, Marc W., Carnation, WA, UNITED STATES
Stolk, John A., Bothell, WA, UNITED STATES
Day, Craig H., Seattle, WA, UNITED STATES
Vedvick, Thomas S., Federal Way, WA, UNITED STATES
Carter, Darrick, Seattle, WA, UNITED STATES
Li, Samuel X., Redmond, WA, UNITED STATES
Wang, Aijun, Issaquah, WA, UNITED STATES
Skeiky, Yasir A. W., Bellevue, WA, UNITED STATES
Hepler, William T., Seattle, WA, UNITED STATES
Henderson, Robert A., Edmonds, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002022248	A1	20020221
APPLICATION INFO.:	US 2001-759143	A1	20010112 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-685166, filed on 10 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-679426, filed on 2 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-657279, filed on 6 Sep 2000, PENDING Continuation-in-part of Ser. No. US 2000-651236, filed on 29 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-636215, filed on 10 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-605783, filed on 27 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-593793, filed on 13 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-570737, filed on 12 May 2000, PENDING Continuation-in-part of Ser. No. US 2000-568100, filed on 9 May 2000, PENDING Continuation-in-part of Ser. No. US 2000-536857, filed on 27 Mar 2000, PENDING Continuation-in-part of Ser. No. US 2000-483672, filed on 14 Jan 2000, PENDING Continuation-in-part of Ser. No. US 1999-443686, filed on 18 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-439313, filed on 12 Nov 1999, PENDING Continuation-in-part of Ser. No. US 1999-352616, filed on 13 Jul 1999, PENDING Continuation-in-part of Ser. No. US 1999-288946, filed on 9 Apr 1999, PENDING Continuation-in-part of Ser. No. US 1999-232149, filed on 15 Jan 1999, PENDING Continuation-in-part of Ser. No. US 1998-159812, filed on 23 Sep 1998, PENDING Continuation-in-part of Ser. No. US 1998-115453, filed on 14 Jul 1998, PENDING Continuation-in-part of Ser. No. US 1998-30607, filed on 25 Feb 1998, GRANTED, Pat. No. US 6262245 Continuation-in-part of Ser. No. US 1998-20956, filed on 9 Feb 1998, GRANTED, Pat. No. US 6261562 Continuation-in-part of Ser. No. US 1997-904804, filed on 1 Aug 1997, ABANDONED Continuation-in-part of Ser. No. US 1997-806099, filed on 25 Feb 1997, ABANDONED

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 7383
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0705] As will be also recognized by the skilled artisan,

polynucleotides of the invention may be single-stranded (coding or **antisense**) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which. . .

DETD [0736] According to another embodiment of the present invention, polynucleotide compositions comprising **antisense** oligonucleotides are provided. **Antisense** oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by. . . which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of **antisense** oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by **antisense** oligonucleotides directed to their respective mRNA sequences (U.S. Pat. No. 5,739,119 and U.S. Pat. No. 5,759,829). Further, examples of **antisense** inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA.sub.A. . . Jun. 15, 1998;57(2):310-20; U.S. Pat. No. 5,801,154; U.S. Pat. No. 5,789,573; U.S. Pat. No. 5,718,709 and U.S. Pat. No. 5,610,288). **Antisense** constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, e.g.. . .

DETD . . . sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the **antisense** oligonucleotides comprise DNA or derivatives thereof In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment,. . . more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of **antisense** compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T.sub.m, binding energy, and relative stability. **Antisense** compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce. . .

DETD [0738] The use of an **antisense** delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic. . . al., Nucleic Acids Res. Jul. 15, 1997;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the **antisense** oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further,. . .

DETD . . . According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of **ribozyme** molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein. . . attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the **ribozyme** prior to chemical reaction.

DETD [0741] The enzymatic nature of a **ribozyme** is advantageous over many technologies, such as **antisense** technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of **ribozyme** necessary to affect a therapeutic treatment is lower than that of an **antisense** oligonucleotide. This advantage reflects the ability of the **ribozyme** to act enzymatically. Thus, a single **ribozyme** molecule is able to cleave many molecules of target RNA. In addition, the **ribozyme** is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding. . . of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a **ribozyme**. Similar mismatches in **antisense** molecules do not prevent their action

(Woolf et al., Proc Natl Acad Sci USA. Aug. 15, 1992;89(16):7305-9). Thus, the specificity of action of a **ribozyme** is greater than that of an **antisense** oligonucleotide binding the same RNA site.

DETD . . . an example of the RNaseP motif is described by Guerrier-Takada et al., Cell. December 1983;35(3 Pt 2):849-57; Neurospora VS RNA **ribozyme** motif is described by Collins (Saville and Collins, Cell. May 18, 1990;61(4):685-96; Saville and Collins, Proc Natl Acad Sci USA.. . . nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the **ribozyme** constructs need not be limited to specific motifs mentioned herein.

DETD [0744] **Ribozyme** activity can be optimized by altering the length of the **ribozyme** binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see e.g., Int. Pat. Appl.. . .

DETD . . . joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of **ribozyme** delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO. . .

DETD [0746] Another means of accumulating high concentrations of a **ribozyme**(s) within cells is to incorporate the **ribozyme** -encoding sequences into a DNA expression vector. Transcription of the **ribozyme** sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA. . .

DETD . . . are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, **Antisense** Nucleic Acid Drug Dev. 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have. . .

DETD [0752] Methods of characterizing the **antisense** binding properties of PNAs are discussed in Rose (Anal Chem. Dec. 15, 1993;65(24):3545-9) and Jensen et al. (Biochemistry. Apr. 22,. . .

DETD . . . of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, **antisense** inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome. . .

DETD . . . WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of **implantation**, the rate and expected duration of release and the nature of the condition to be treated or prevented.

DETD . . . subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, **placenta**, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This. . .

DETD [0943] P703P was found to show some homology to previously identified proteases, such as thrombin. The **thrombin receptor** has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of **thrombin receptor antisense** cDNA has been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against **thrombin receptor** inhibit **thrombin receptor** activation and thrombin-induced platelet activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P. . .

DETD . . . and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an **antisense** cloning primer that contains an EcoRi site. DNA amplification was performed using 5 .mu.l 10.times.Pfu buffer, 1 .mu.l 20 mM. . .

DETD . . . to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an **antisense** cloning primer that contains an EcoRI site and a stop codon. DNA amplification was

performed essentially as described above. The. . .

DETD . . . and AW053 (SEQ ID NO: 850). AW042 is a sense cloning primer that contains a EcoRI site. AW053 is an **antisense** primer with stop and Xho I sites. DNA amplification was performed essentially as described above. The resulting PCR product was. . .

DETD . . . AW081 (SEQ ID NO: 815 and 816). AW080 is a sense cloning primer with an NdeI site. AW081 is an **antisense** cloning primer with a XhoI site. The PCR-amplified P788P, as well as the vector pCRX1, were digested with NdeI and. . .

DETD . . . (SEQ ID NO: 820 and 821, respectively). AW056 is a sense cloning primer with an EcoRI site. AW057 is an **antisense** primer with stop and XhoI sites. The amplified P501S fragment and Ra12/pCRX1 were digested with EcoRI and XhoI and then. . .

DETD . . . was used. The primer of SEQ ID NO: 828 created a 5' NcoI site and added a start codon. The **antisense** primer of SEQ ID NO: 829 creates a XhoI site on P510S C terminal fragment. Clones were confirmed by sequencing.. . .

DETD . . . primer with an NdeI site for use in ligating into pPDM. The primer of SEQ ID NO: 831 is an **antisense** primer with an added XhoI site for use in ligating into pPDM. The resulting fragment was cloned to pPDM at. . .

DETD . . . were as follows: TCR Valpha-6 5'(sense): GGATCC-GCCGCCACC-ATGTCACTTTCTAGCCTGCT (SEQ ID NO: 899) BamHI site Kozak TCR alpha sequence TCR alpha 3' (**antisense**): GTCGAC-TCAGCTGGACCACAGCCGCAG (SEQ ID NO: 900) SalI site TCR alpha constant sequence TCR Vbeta-7. 5'(sense): GGATCC-GCCGCCACC-ATGGGCTGCAGGCTGCTCT (SEQ ID NO: 901) BamHI site Kozak TCR alpha sequence TCR beta 3' (**antisense**): GTCGAC-TCAGAAATCCTTTCTCTTGAC (SEQ ID NO: 902) SalI site TCR beta constant sequence. Standard 35 cycle RT-PCR reactions were established using cDNA. . .

L14 ANSWER 28 OF 70 USPATFULL

ACCESSION NUMBER:	2002:16850 USPATFULL
TITLE:	Human stress array
INVENTOR(S):	Chenchik, Alex, Palo Alto, CA, UNITED STATES Lukashev, Matvey E., Newton, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002009730	A1	20020124
APPLICATION INFO.:	US 2001-782909	A1	20010213 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-441920, filed on 17 Nov 1999, UNKNOWN

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Bret E. Field, BOZICEVIC, FIELD & FRANCIS LLP, 200 Middlefield Road, Suite 200, Menlo Park, CA, 94025

NUMBER OF CLAIMS: 36

EXEMPLARY CLAIM: 1

LINE COUNT: 2377

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . in Table 1 were amplified from quick-clone cDNA (CLONTECH) in 236 separate test tubes using a combination of sense and **antisense** gene-specific primers capable of amplifying the specific gene fragments of interest as specified in Table 1. Amplification was conducted in a 100-.mu.l volume containing 2 .mu.l of mixture of 10 Quick-clone cDNA from **placenta**, brain, liver, lung, leukocytes, spleen, skeletal muscle, testis, kidney and ovary (CLONTECH), 40 mM Tricine-KOH (pH 9.2 at 22.degree. C.),. . . mM KOAc, 75 .mu.g/ml BSA, 200 .mu.M of each dATP, dGTP, dCTP and dTTP, 0.2 .mu.M of each sense and **antisense** gene-specific primers and 2 .mu.l of KlenTaq Polymerase mix. Temperature parameters of the PCR reactions were as follows: 1 min. . . sequence analysis. The ds cDNA inserts with the sequence corresponding 236 genes were amplified by PCR using a combination of **antisense** and sense gene-specific

primers, as described above. The ds cDNA was denatured by adding 1 .mu.l of 10.times.denaturing solution (1. . .

DETD . . . Al receptor (ADORA1) 556143
P30542

62 orphan hormone nuclear receptor Z30425
Q14994

63 adenosine A3 receptor (ADORA3) X76981
P33765

66 **thrombin receptor** (TR); **F2R**; PAR1
M62424 P25116

67 transforming growth factor beta receptor III (TGF beta receptor III; TGFR3); betaglycan L07594
Q03167

72 GATA-binding. . .

L14 ANSWER 29 OF 70 USPATFULL

ACCESSION NUMBER: 2002:254200 USPATFULL
TITLE: DNA encoding the human serine protease T
INVENTOR(S): Darrow, Andrew, Lansdale, PA, United States
Qi, Jenson, Branchburg, NJ, United States
Andrade-Grodon, Patricia, Doylestown, PA, United States
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6458564	B1	20021001	
APPLICATION INFO.:	US 1999-386653		19990831	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Achutamurthy, Ponnathapu
ASSISTANT EXAMINER: Moore, William W.
LEGAL REPRESENTATIVE: Wallen, III, John W.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 2073
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Nucleotide sequences that are complementary to the protease T encoding DNA sequence can be synthesized for **antisense** therapy. These **antisense** molecules may be DNA, stable derivatives of DNA such as phosphorothioates or methylphosphonates, RNA, stable derivatives of RNA such as 2'-O-alkylRNA, or other protease T **antisense** oligonucleotide mimetics, protease T **antisense** molecules may be introduced into cells by microinjection, liposome encapsulation or by expression from vectors harboring the **antisense** sequence, protease T **antisense** therapy may be particularly useful for the treatment of diseases where it is beneficial to reduce protease T expression or. . .

DETD . . . is highly restricted to specific tissues and cell types. The tissue types found to express the protease T transcript are **placenta**, stomach, testis, retina, fibroblasts, spinal cord, and several regions of the brain. Protease T mRNA is also found in leukocytes. . .

DETD Ishii, K., Hein, L., Kobilka, B., and Coughlin, S. R. (1993). Kinetics of **thrombin receptor** cleavage on intact cells. Relation to signaling. J. Biol. Chem. 268, 9780-6.

L14 ANSWER 30 OF 70 USPATFULL

ACCESSION NUMBER: 2002:230959 USPATFULL
TITLE: Testis expressed polypeptide
INVENTOR(S): Ruben, Steven M., Olney, MD, United States
Rosen, Craig A., Laytonsville, MD, United States
Zeng, Zhizhen, Gaithersburg, MD, United States
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, United

States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6448230	B1	20020910
APPLICATION INFO.:	US 1998-152060		19980911 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. WO 1998-US4858, filed on 12 Mar 1998		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-40762P	19970314 (60)
	US 1997-40710P	19970314 (60)
	US 1997-50934P	19970530 (60)
	US 1997-48100P	19970530 (60)
	US 1997-48357P	19970530 (60)
	US 1997-48189P	19970530 (60)
	US 1997-57765P	19970905 (60)
	US 1997-48970P	19970606 (60)
	US 1997-68368P	19971219 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Davenport, Avis M.
LEGAL REPRESENTATIVE: Human Genome Sciences Inc.
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 7777
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM This gene is expressed primarily in **placenta**, and to a lesser extent, in T-cells.

SUMM . . . this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g.immune, hematopoietic, **placenta**, and T-cells, and cancerous and wounded tissues) or bodily fluids (e.g.lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal. . .

SUMM The translation product of this gene shares sequence homology with a frog **thrombin receptor** [Xenopus laevis]. Moreover, another group recently cloned this same gene, also recognizing the homology to thrombing receptors. (See Accession NO:. . .

SUMM . . . effects. Additionally, neovascularization and various cell-type specific proliferation effects have been seen. The fact that this clone was isolated from **placenta** RNA may make this an interesting gene to characterize. The known neurokinins are expressed in either the central nervous system. . .

SUMM This gene is expressed primarily in human **placenta** and to a lesser extent in soares **placenta**.

SUMM . . . of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., **placenta**, and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine,. . .

SUMM This gene is expressed primarily in the testes and to a lesser extent in the lung, tonsils, **placenta**, and rhabdomyosarcoma.

SUMM . . . for diagnosis of diseases and conditions which include, but are not limited to, diseases related to the testes, lung, tonsils, **placenta**, and tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of. . . a number of disorders of the above tissues or cells, particularly of the diseases related to the testes, lung, tonsils, **placenta**, and tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., testes and other reproductive tissue, lung, tonsils, **placenta**, and striated muscle, and cancerous and wounded tissues) or bodily fluids (e.g.,

seminal fluid, serum, plasma, urine, synovial fluid or. . .

SUMM . . . and polypeptides corresponding to the gene are useful for diagnosis and treatment of diseases related to the testes, lung, tonsils, **placenta**, and tumors. More specifically, the tissue distribution indicates that the protein product of this clone is useful for the treatment. . .

SUMM This gene is expressed primarily in **placenta** and human amygdala, and to a lesser extent in adult brain, primary dendritic cells, keratinocytes, activated monocytes, human cerebellum, and. . .

SUMM . . . of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., **placenta**, amygdala, brain and other tissue of the nervous system, dendritic cells, blood cells, keratinocytes, and cancerous and wounded tissues) or. . .

SUMM In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or **antisense** DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides. . . (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (**antisense**--Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while **antisense** RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design **antisense** or triple helix polynucleotides in an effort to treat disease.

DETD . . . that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, **antisense**.

DETD **Antisense** technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a. . .

DETD For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously **antisense** polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the **antisense** polynucleotide is provided in Example 23.

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=> s l6 and (placenta and implantation)
L15          17 L6 AND (PLACENTA AND IMPLANTATION)

=> dup rem l15
PROCESSING COMPLETED FOR L15
L16          17 DUP REM L15 (0 DUPLICATES REMOVED)

=> d l16 ibib abs tot

L16  ANSWER 1 OF 17  USPATFULL
ACCESSION NUMBER:        2002:308355  USPATFULL
TITLE:                   Regulation of vascular endothelium using BMX tyrosine
                         kinase
INVENTOR(S):             Ekman, Niklas, Helsinki, FINLAND
                         Arighi, Elena, Helsinki, FINLAND
                         Vastrik, Imre, London, UNITED KINGDOM
                         Tamagnone, Luca, Torino, ITALY
                         Alitalo, Kari, Espoo, FINLAND

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2002173481      A1   20021121
APPLICATION INFO.:       US 2002-186399     A1   20020701  (10)
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RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-538445, filed on 29 Mar 2000, PENDING Continuation of Ser. No. US 1998-104863, filed on 25 Jun 1998, ABANDONED Continuation-in-part of Ser. No. US 1994-320432, filed on 7 Oct 1994, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: David A. Gass, MARSHALL, GERSTEIN & BORUN, Sears Tower, 233 S. Wacker Drive, Suite 6300, Chicago, IL, 60606-6357
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 1184

AB Vascular endothelia are subject to atherosclerotic and arteriostenotic effects transduced by molecules, such as thrombin, IL-3 and VEGF which can lead to vessel occlusion or stenosis. An endothelial signaling pathway involving the Bmx tyrosine kinase contributes to normal endothelial nonthrombogenic, inflammatory and growth conditions of arterial vessels, and regulation of the pathway can treat or prevent pathological conditions in the vessel walls.

L16 ANSWER 2 OF 17 USPATFULL
ACCESSION NUMBER: 2002:307870 USPATFULL
TITLE: 28 human secreted proteins
INVENTOR(S): Ruben, Steven M., Olney, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Zeng, Zhizhen, Lansdale, PA, UNITED STATES
Kyaw, Hla, Frederick, MD, UNITED STATES
Fischer, Carrie L., Burke, VA, UNITED STATES
Li, Haodong, Gaithersburg, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
Gentz, Reiner L., Rockville, MD, UNITED STATES
Wei, Ying-Fei, Berkeley, CA, UNITED STATES
Moore, Paul A., Germantown, MD, UNITED STATES
Young, Paul E., Gaithersburg, MD, UNITED STATES
Greene, John M., Gaithersburg, MD, UNITED STATES
Ferrie, Ann M., Tewksbury, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002172994	A1	20021121
APPLICATION INFO.:	US 2001-852797	A1	20010511 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-152060, filed on 11 Sep 1998, PENDING Continuation-in-part of Ser. No. WO 1998-US4858, filed on 12 Mar 1998, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-265583P	20010202 (60)
	US 1997-40762P	19970314 (60)
	US 1997-40710P	19970314 (60)
	US 1997-50934P	19970530 (60)
	US 1997-48100P	19970530 (60)
	US 1997-48357P	19970530 (60)
	US 1997-48189P	19970530 (60)
	US 1997-57765P	19970905 (60)
	US 1997-48970P	19970606 (60)
	US 1997-68368P	19971219 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 17794
AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

L16 ANSWER 3 OF 17 USPATFULL
ACCESSION NUMBER: 2002:206605 USPATFULL
TITLE: Novel nucleic acids and polypeptides
INVENTOR(S): Tang, Y. Tom, San Jose, CA, UNITED STATES
Zhou, Ping, Cupertino, CA, UNITED STATES
Goodrich, Ryle, San Jose, CA, UNITED STATES
Liu, Chenghua, San Jose, CA, UNITED STATES
Asundi, Vinod, Foster City, CA, UNITED STATES
Wang, Jian-Rui, Cupertino, CA, UNITED STATES
Wang, Dunrui, Poway, CA, UNITED STATES
Yamazaki, Victoria, Redwood Shores, CA, UNITED STATES
Ujwal, Manusha L., Gaithersburg, MD, UNITED STATES
Drmanac, Radoje T., Palo Alto, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002111302	A1	20020815	
APPLICATION INFO.:	US 2000-728952	A1	20001130	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Ivor R. Elrifi, Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C, One Financial Center, Boston, MA, 02111
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
LINE COUNT: 4863
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides novel nucleic acids, novel polypeptide sequences encoded by these nucleic acids and uses thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 4 OF 17 USPATFULL
ACCESSION NUMBER: 2002:191522 USPATFULL
TITLE: G protein coupled receptor kinase 5 (GRK5) and its uses
INVENTOR(S): Delaney, Allen, Vancouver, CANADA
Yoganathan, Thillainathan, Richmond, CANADA

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002102587	A1	20020801	
APPLICATION INFO.:	US 2001-972694	A1	20011004	(9)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2001-US21479, filed on 20 Sep 2001, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-237423P	20001002 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PAMELA J. SHERWOOD, Bozicevic, Field and Francis LLP, Suite 200, 200 Middlefield Road, Menlo Park, CA, 94025
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1

LINE COUNT: 1356
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Detection of GRK5 expression in cancers is useful as a diagnostic, for determining the effectiveness of drugs, and determining patient prognosis. GRK5 further provides a target for screening pharmaceutical agents effective in inhibiting the growth or metastasis of tumor cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 5 OF 17 USPATFULL
ACCESSION NUMBER: 2002:165193 USPATFULL
TITLE: Nucleic acids, proteins, and antibodies
INVENTOR(S): Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002086822	A1	20020704	
APPLICATION INFO.:	US 2001-764886	A1	20010117	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-179065P	20000131	(60)
	US 2000-180628P	20000204	(60)
	US 2000-214886P	20000628	(60)
	US 2000-217487P	20000711	(60)
	US 2000-225758P	20000814	(60)
	US 2000-220963P	20000726	(60)
	US 2000-217496P	20000711	(60)
	US 2000-225447P	20000814	(60)
	US 2000-218290P	20000714	(60)
	US 2000-225757P	20000814	(60)
	US 2000-226868P	20000822	(60)
	US 2000-216647P	20000707	(60)
	US 2000-225267P	20000814	(60)
	US 2000-216880P	20000707	(60)
	US 2000-225270P	20000814	(60)
	US 2000-251869P	20001208	(60)
	US 2000-235834P	20000927	(60)
	US 2000-234274P	20000921	(60)
	US 2000-234223P	20000921	(60)
	US 2000-228924P	20000830	(60)
	US 2000-224518P	20000814	(60)
	US 2000-236369P	20000929	(60)
	US 2000-224519P	20000814	(60)
	US 2000-220964P	20000726	(60)
	US 2000-241809P	20001020	(60)
	US 2000-249299P	20001117	(60)
	US 2000-236327P	20000929	(60)
	US 2000-241785P	20001020	(60)
	US 2000-244617P	20001101	(60)
	US 2000-225268P	20000814	(60)
	US 2000-236368P	20000929	(60)
	US 2000-251856P	20001208	(60)
	US 2000-251868P	20001208	(60)
	US 2000-229344P	20000901	(60)
	US 2000-234997P	20000925	(60)
	US 2000-229343P	20000901	(60)
	US 2000-229345P	20000901	(60)
	US 2000-229287P	20000901	(60)
	US 2000-229513P	20000905	(60)
	US 2000-231413P	20000908	(60)
	US 2000-229509P	20000905	(60)
	US 2000-236367P	20000929	(60)

	US 2000-237039P	20001002	(60)
	US 2000-237038P	20001002	(60)
	US 2000-236370P	20000929	(60)
	US 2000-236802P	20001002	(60)
	US 2000-237037P	20001002	(60)
	US 2000-237040P	20001002	(60)
	US 2000-240960P	20001020	(60)
	US 2000-239935P	20001013	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
LINE COUNT: 20931
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 6 OF 17 USPATFULL
ACCESSION NUMBER: 2002:157081 USPATFULL
TITLE: Compositions and methods for the therapy and diagnosis of prostate cancer
INVENTOR(S): Xu, Jiangchun, Bellevue, WA, UNITED STATES
Dillon, Davin C., Issaquah, WA, UNITED STATES
Mitcham, Jennifer L., Redmond, WA, UNITED STATES
Harlocker, Susan L., Seattle, WA, UNITED STATES
Jiang, Yuqiu, Kent, WA, UNITED STATES
Kalos, Michael D., Seattle, WA, UNITED STATES
Fanger, Gary R., Mill Creek, WA, UNITED STATES
Retter, Marc W., Carnation, WA, UNITED STATES
Stolk, John A., Bothell, WA, UNITED STATES
Day, Craig H., Seattle, WA, UNITED STATES
Vedvick, Thomas S., Federal Way, WA, UNITED STATES
Carter, Darrick, Seattle, WA, UNITED STATES
Li, Samuel X., Redmond, WA, UNITED STATES
Wang, Aijun, Issaquah, WA, UNITED STATES
Skeiky, Yasir A. W., Bellevue, WA, UNITED STATES
Hepler, William T., Seattle, WA, UNITED STATES
Henderson, Robert A., Edmonds, WA, UNITED STATES
Hural, John, Bainbridge Island, WA, UNITED STATES
McNeill, Patricia D., Federal Way, WA, UNITED STATES
Houghton, Raymond L., Bothell, WA, UNITED STATES
de Bassols, Carlota Vinals, Rixensart, BELGIUM

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002081680	A1	20020627	
APPLICATION INFO.:	US 2001-822827	A1	20010328	(9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-780669, filed on 9 Feb 2001, PENDING Continuation-in-part of Ser. No. US 2000-679272, filed on 4 Oct 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-157455P	20000417 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 7692
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis prevention and/or treatment of diseases, particularly prostate cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 7 OF 17 USPATFULL
ACCESSION NUMBER: 2002:149131 USPATFULL
TITLE: 28 human secreted proteins
INVENTOR(S): Ruben, Steven M., Olney, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Zeng, Zhizhen, Lansdale, PA, UNITED STATES
Kyaw, Hla, Frederick, MD, UNITED STATES
Fischer, Carrie L., Burke, VA, UNITED STATES
Li, Haodong, Gaithersburg, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
Gentz, Reiner L., Rockville, MD, UNITED STATES
Wei, Ying-Fei, Berkeley, CA, UNITED STATES
Moore, Paul A., Germantown, MD, UNITED STATES
Young, Paul E., Gaithersburg, MD, UNITED STATES
Greene, John M., Gaithersburg, MD, UNITED STATES
Ferrie, Ann M., Tewksbury, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002077287	A1	20020620
APPLICATION INFO.:	US 2001-852659	A1	20010511 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-152060, filed on 11 Sep 1998, UNKNOWN
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 17779
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 8 OF 17 USPATFULL
ACCESSION NUMBER: 2002:148614 USPATFULL
TITLE: 28 human secreted proteins
INVENTOR(S): Ruben, Steven M., Olney, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Zeng, ZhiZhen, Lansdale, PA, UNITED STATES
Kyaw, Hla, Frederick, MD, UNITED STATES
Fischer, Carrie L., Burke, VA, UNITED STATES
Li, Haodong, Gaithersburg, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
Gentz, Reiner L., Rockville, MD, UNITED STATES
Wei, Ying-Fei, Berkeley, CA, UNITED STATES
Moore, Paul A., Germantown, MD, UNITED STATES
Young, Paul E., Gaithersburg, MD, UNITED STATES
Greene, John M., Gaithersburg, MD, UNITED STATES
Ferrie, Ann M., Painted Post, NY, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002076756	A1	20020620	
APPLICATION INFO.:	US 2001-853161	A1	20010511	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-265583P	20010202 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 17788
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 9 OF 17 USPATFULL
ACCESSION NUMBER: 2002:99081 USPATFULL
TITLE: Compositions and methods for the therapy and diagnosis of prostate cancer
INVENTOR(S): Xu, Jiangchun, Bellevue, WA, UNITED STATES
Dillon, Davin C., Issaquah, WA, UNITED STATES
Mitcham, Jennifer L., Redmond, WA, UNITED STATES
Harlocker, Susan L., Seattle, WA, UNITED STATES
Jiang, Yuqiu, Kent, WA, UNITED STATES
Kalos, Michael D., Seattle, WA, UNITED STATES
Fanger, Gary R., Mill Creek, WA, UNITED STATES
Retter, Marc W., Carnation, WA, UNITED STATES
Stolk, John A., Bothell, WA, UNITED STATES
Day, Craig H., Seattle, WA, UNITED STATES
Vedvick, Thomas S., Federal Way, WA, UNITED STATES
Carter, Darrick, Seattle, WA, UNITED STATES
Li, Samuel X., Redmond, WA, UNITED STATES
Wang, Aijun, Issaquah, WA, UNITED STATES
Skeiky, Yasir A. W., Bellevue, WA, UNITED STATES
Hepler, William T., Seattle, WA, UNITED STATES

Henderson, Robert A., Edmonds, WA, UNITED STATES
Hural, John, Bainbridge Island, WA, UNITED STATES
McNeill, Patricia D., Des Moines, WA, UNITED STATES
Houghton, Raymond L., Bothell, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002051977	A1	20020502
APPLICATION INFO.:	US 2001-780669	A1	20010209 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-759143, filed on 12 Jan 2001, PENDING Continuation-in-part of Ser. No. US 2000-709729, filed on 9 Nov 2000, PENDING Continuation-in-part of Ser. No. US 2000-685166, filed on 10 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-679426, filed on 2 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-657279, filed on 6 Sep 2000, PENDING Continuation-in-part of Ser. No. US 2000-651236, filed on 29 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-636215, filed on 10 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-605783, filed on 27 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-593793, filed on 13 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-510737, filed on 1 May 2000, GRANTED, Pat. No. US 6219981 Continuation-in-part of Ser. No. US 2000-568100, filed on 9 May 2000, PENDING Continuation-in-part of Ser. No. US 2000-536857, filed on 27 Mar 2000, PENDING Continuation-in-part of Ser. No. US 2000-483672, filed on 14 Jan 2000, PENDING Continuation-in-part of Ser. No. US 1999-443686, filed on 18 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-439313, filed on 12 Nov 1999, PENDING Continuation-in-part of Ser. No. US 1999-352616, filed on 13 Jul 1999, PENDING Continuation-in-part of Ser. No. US 1999-288946, filed on 9 Apr 1999, PENDING Continuation-in-part of Ser. No. US 1999-232149, filed on 15 Jan 1999, PENDING Continuation-in-part of Ser. No. US 1998-159812, filed on 23 Sep 1998, PENDING Continuation-in-part of Ser. No. US 1998-115453, filed on 14 Jul 1998, PENDING Continuation-in-part of Ser. No. US 1998-30607, filed on 25 Feb 1998, GRANTED, Pat. No. US 6262245 Continuation-in-part of Ser. No. US 1998-20956, filed on 9 Feb 1998, GRANTED, Pat. No. US 6261562 Continuation-in-part of Ser. No. US 1997-904804, filed on 1 Aug 1997, ABANDONED Continuation-in-part of Ser. No. US 1997-806099, filed on 25 Feb 1997, ABANDONED Continuation-in-part of Ser. No. WO 1998-US3492, filed on 25 Feb 1998, UNKNOWN Continuation-in-part of Ser. No. WO 1999-US15838, filed on 14 Jul 1999, UNKNOWN

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 7556
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed

compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly prostate cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 10 OF 17 USPATFULL

ACCESSION NUMBER: 2002:37531 USPATFULL

TITLE: Compositions and methods for the therapy and diagnosis of prostate cancer

INVENTOR(S): Xu, Jiangchun, Bellevue, WA, UNITED STATES
Dillon, Davin C., Issaquah, WA, UNITED STATES
Mitcham, Jennifer L., Redmond, WA, UNITED STATES
Harlocker, Susan L., Seattle, WA, UNITED STATES
Jiang, Yuqiu, Kent, WA, UNITED STATES
Kalos, Michael D., Seattle, WA, UNITED STATES
Fanger, Gary R., Mill Creek, WA, UNITED STATES
Retter, Marc W., Carnation, WA, UNITED STATES
Stolk, John A., Bothell, WA, UNITED STATES
Day, Craig H., Seattle, WA, UNITED STATES
Vedvick, Thomas S., Federal Way, WA, UNITED STATES
Carter, Darrick, Seattle, WA, UNITED STATES
Li, Samuel X., Redmond, WA, UNITED STATES
Wang, Aijun, Issaquah, WA, UNITED STATES
Skeiky, Yasir A. W., Bellevue, WA, UNITED STATES
Hepler, William T., Seattle, WA, UNITED STATES
Henderson, Robert A., Edmonds, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002022248	A1	20020221
APPLICATION INFO.:	US 2001-759143	A1	20010112 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-685166, filed on 10 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-679426, filed on 2 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-657279, filed on 6 Sep 2000, PENDING Continuation-in-part of Ser. No. US 2000-651236, filed on 29 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-636215, filed on 10 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-605783, filed on 27 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-593793, filed on 13 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-570737, filed on 12 May 2000, PENDING Continuation-in-part of Ser. No. US 2000-568100, filed on 9 May 2000, PENDING Continuation-in-part of Ser. No. US 2000-536857, filed on 27 Mar 2000, PENDING Continuation-in-part of Ser. No. US 2000-483672, filed on 14 Jan 2000, PENDING Continuation-in-part of Ser. No. US 1999-443686, filed on 18 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-439313, filed on 12 Nov 1999, PENDING Continuation-in-part of Ser. No. US 1999-352616, filed on 13 Jul 1999, PENDING Continuation-in-part of Ser. No. US 1999-288946, filed on 9 Apr 1999, PENDING Continuation-in-part of Ser. No. US 1999-232149, filed on 15 Jan 1999, PENDING Continuation-in-part of Ser. No. US 1998-159812, filed on 23 Sep 1998, PENDING Continuation-in-part of Ser. No. US 1998-115453, filed on 14 Jul 1998, PENDING Continuation-in-part of Ser. No. US 1998-30607, filed on 25 Feb 1998, GRANTED, Pat. No. US 6262245 Continuation-in-part of Ser. No. US 1998-20956, filed on 9 Feb 1998, GRANTED, Pat. No. US 6261562 Continuation-in-part of Ser. No. US 1997-904804, filed on 1 Aug 1997, ABANDONED Continuation-in-part of Ser. No. US 1997-806099, filed on 25 Feb 1997, ABANDONED

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 7383
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly prostate cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 11 OF 17 USPATFULL
ACCESSION NUMBER: 2001:93478 USPATFULL
TITLE: Urokinase-type plasminogen activator receptor
INVENTOR(S): Dan.o slashed. , Keld, Charlottenlund, Denmark
Blasi, Francesco, Charlottenlund, Denmark
Roldan, Ann Louring, Vallensb.ae butted.k, Denmark
Cubellis, Maria Vittoria, Naples, Italy
Masucci, Maria Teresa, Naples, Italy
Appella, Ettore, Chevy Chase, MD, United States
Schleuning, W.D., Berlin, Germany, Federal Republic of
Behrendt, Niels, Bagsv.ae butted.rd, Denmark
R.o slashed.nne, Ebbe, Copenhagen, Denmark
Kristensen, Peter, Copenhagen, Denmark
Pollanen, Jari, Espoo, Finland
Salonen, Eeva-Marjatta, Espoo, Finland
Stephens, Ross W., Vantaa, Finland
Tapiovaara, Hannele, Helsinki, Finland
Vaheri, Antti, Kauniainen, Finland
M.o slashed.ller, Lisbeth Birk, Bagsv.ae butted.rd, Denmark
Ellis, Vincent, Copenhagen, Denmark
Lund, Leif R.o slashed.ge, Copenhagen, Denmark
Ploug, Michael, Copenhagen, Denmark
Pyke, Charles, S.o slashed.borg, Denmark
Patthy, Laszlo, Budapest, Hungary
PATENT ASSIGNEE(S): Cancerforskningsfondet af 1989, Denmark (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6248712	B1	20010619
APPLICATION INFO.:	US 1995-442108		19950516 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-319052, filed on 6 Oct 1994, now patented, Pat. No. US 5891644 Continuation of Ser. No. US 824189, now abandoned Continuation-in-part of Ser. No. US 1989-374854, filed on 3 Jul 1989, now abandoned Continuation-in-part of Ser. No. US 1989-334613, filed on 7 Apr 1989, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Feisee, Lila
ASSISTANT EXAMINER: Basi, Nirmal S.
LEGAL REPRESENTATIVE: Cooper, Iver P.
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 86 Drawing Figure(s); 54 Drawing Page(s)
LINE COUNT: 6444
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Activation of plasminogen to plasmin is inhibited by preventing the binding of a receptor binding form of urokinase-type plasminogen activator to a urokinase-type plasminogen activator receptor in a mammal, thereby preventing the urokinase-type plasminogen activator from converting plasminogen into plasmin. DNA fragments which encode for soluble, active fragments of the urokinase-type plasminogen activator receptor are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:117151 CAPLUS
DOCUMENT NUMBER: 132:175814
TITLE: Treatment of invasive cells with **antisense** or antibody inhibitors of protease-activated receptors
INVENTOR(S): Bar-Shavit, Rachel
PATENT ASSIGNEE(S): Hadasit Medical Research Services & Development Company Ltd., Israel
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000008150	A1	20000217	WO 1999-IL79	19990205
W: CA, JP, RU, US				
CA 2339413	AA	20000217	CA 1999-2339413	19990205

PRIORITY APPLN. INFO.: IL 1998-125698 A 19980807
WO 1999-IL79 W 19990205

AB A method for treating metastatic tumor cells of a subject is disclosed. The method comprises administrating to the subject an **antisense** mol. comprising a nucleotide sequence which is complementary to an RNA sequence of a protease-activated receptor (PAR) protein, or an antibody mol. capable of binding to a PAR protein. A method is also described for the treatment of disorders involving the **implantation** of a **placenta** in a female subject comprising administrating to the subject the **antisense** mol. **Thrombin receptor** is expressed in breast carcinoma cell lines, human breast tissue specimens, and in trophoblast cells during **implantation** of **placenta**. The **antisense** mol. for human **thrombin receptor** and a pharmaceutical compn. comprising it are provided.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 13 OF 17 USPATFULL
ACCESSION NUMBER: 2000:117278 USPATFULL
TITLE: Antibodies and their use
INVENTOR(S): Dan.o slashed., Keld, Charlottenlund, Denmark
R.o slashed.nne, Ebbe, Copenhagen, Denmark
Behrendt, Niels, Bagsvaerd, Denmark
Ellis, Vincent, Copenhagen, Denmark
H.o slashed.yer-Hansen, Gunilla, Gentofte, Denmark
Pyke, Charles, S.o slashed.borg, Denmark
Bruenner, Nils, Virum, Denmark
PATENT ASSIGNEE(S): Cancerforskiningsfonden af 1989, Copenhagen, Denmark (non-U.S. corporation)

NUMBER	KIND	DATE

PATENT INFORMATION: US 6113897 20000905
APPLICATION INFO.: US 1995-580166 19951228 (8)
RELATED APPLN. INFO.: Division of Ser. No. US 1993-85122, filed on 17 Jun 1993, now patented, Pat. No. US 5519120 which is a continuation-in-part of Ser. No. US 1991-824189, filed on 6 Dec 1991, now abandoned which is a continuation of Ser. No. WO 1990-DK90, filed on 9 Apr 1990 which is a continuation-in-part of Ser. No. US 1989-374854, filed on 3 Jul 1989, now abandoned which is a continuation-in-part of Ser. No. US 1989-334613, filed on 7 Apr 1989 which is a continuation-in-part of Ser. No. WO 1991-DK319, filed on 18 Oct 1991 which is a continuation-in-part of Ser. No. WO 1990-DK270, filed on 18 Oct 1990
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Chin, Christopher L.
ASSISTANT EXAMINER: Devi, S.
LEGAL REPRESENTATIVE: Cooper, Iver P.
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 61 Drawing Figure(s); 35 Drawing Page(s)
LINE COUNT: 5386
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A monoclonal or polyclonal antibody directed against urokinase plasminogen activator receptor (u-PAR), or a subsequence, analogue or glycosylation variant thereof. Antibodies are disclosed which react with free u-PAR or with complexes between u-PA and u-PAR and which are capable of 1) catching u-PAR in ELISA, or 2) detecting u-PAR, e.g. in blotting, or 3) in radioimmunoprecipitation assay precipitate purified u-PAR in intact or fragment form, or 4) is useful for immunohistochemical detection of u-PAR, e.g. in immunostaining of cancer cells, such as in tissue sections at the invasive front, or 5) inhibits the binding of pro-u-PA and active u-PA and thereby inhibits cell surface plasminogen activation. Methods are disclosed 1) for detecting or quantifying u-PAR, 2) for targeting a diagnostic to a cell containing a u-PAR on the surface, 3) for preventing or counteracting proteolytic activity in a mammal. Methods for for selecting a substance suitable for inhibiting u-PA/u-PAR interaction, for preventing or counteracting localized proteolytical activity in a mammal, for inhibiting the invasion and/or metastasis comprise the use of the antibodies and of nude mice inoculated with human cancer cells which are known to invade and/or metastasize in mice and having a distinct color, f.x. obtained by means of an enzyme and a chromogenic substrate for the enzyme, the color being different from the cells of the mouse.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 14 OF 17 USPATFULL
ACCESSION NUMBER: 2000:18280 USPATFULL
TITLE: Nucleic acid sequence of senescence asssociated gene
INVENTOR(S): Funk, Walter, Hayward, CA, United States
PATENT ASSIGNEE(S): Geron Corporation, Menlo Park, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6025194		20000215	
APPLICATION INFO.:	US 1997-974180		19971119	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Huff, Sheela
ASSISTANT EXAMINER: Bansal, Geetha P.
LEGAL REPRESENTATIVE: Earp, David J., Kaster, Kevin
NUMBER OF CLAIMS: 10

EXEMPLARY CLAIM: 1,6
LINE COUNT: 4667
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Human gene GC6 is expressed more abundantly in senescent cells than young cells. Isolated, purified, and recombinant nucleic acids and proteins corresponding to the human GC6 gene and its mRNA and protein products, as well as peptides and antibodies corresponding to the GC6 protein can be used to identify senescent cells, distinguish between senescent and young cells, identify agents that alter senescent gene expression generally and GC6 expression specifically; such agents as well as GC6 gene and gene products and products corresponding thereto can be used to prevent and treat diseases and conditions relating to cell senescence.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 15 OF 17 USPATFULL

ACCESSION NUMBER:	1999:43412 USPATFULL
TITLE:	Vectors and methods for recombinant production of uPA-binding fragments of the human urokinase-type plasminogen receptor (uPAR)
INVENTOR(S):	Dan.o slashed. , Keld, Charlottenlund, Denmark Blasi, Francesco, Charlottenlund, Denmark Roldan, Ann Louring, Vallensb.ae butted.k, Denmark Cubellis, Maria Vittoria, Napoli, Italy Masucci, Maria Teresa, Napoli, Italy Appella, Ettore, Chevy Chase, MD, United States Schleuning, Wolf-Dieter, Berlin, Germany, Federal Republic of Behrendt, Niels, Bagsv.ae butted.rd, Denmark R.o slashed.nne, Ebbe, Copenhagen, Denmark Kristensen, Peter, Copenhagen, Denmark Pollanen, Jari, Espoo, Finland Salonen, Eeva-Marjatta, Espoo, Finland Stephens, Ross W., Helsinki, Finland Tapiovaara, Hannele, Helsinki, Finland Vaheri, Antti, Kauniainen, Finland M.o slashed.ller, Lisbeth Birk, Bagsv.ae butted.rd, Denmark Ellis, Vincent, Copenhagen, Denmark Lund, Leif R.o slashed.ge, Copenhagen, Denmark Ploug, Michael, Copenhagen, Denmark Pyke, Charles, S.o slashed.borg, Denmark Patthy, Laszlo, Budapest, Hungary
PATENT ASSIGNEE(S):	Cancerforskningsfondet af 1989, Copenhagen K, Denmark (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5891664		19990406
APPLICATION INFO.:	US 1994-319052		19941006 (8)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1991-824189, filed on 6 Dec 1991, now abandoned which is a continuation-in-part of Ser. No. US 1989-374854, filed on 3 Jul 1989, now abandoned which is a continuation-in-part of Ser. No. US 1989-334613, filed on 7 Apr 1989, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Walsh, Stephen G.
ASSISTANT EXAMINER:	Fitzgerald, David L.
LEGAL REPRESENTATIVE:	Cooper, Iver P.
NUMBER OF CLAIMS:	22
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	83 Drawing Figure(s); 53 Drawing Page(s)
LINE COUNT:	6449

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Activation of plasminogen to plasma is inhibited by preventing the binding of a receptor binding form of urokinase-type plasminogen activator to a urokinase-type plasminogen activator receptor in a mammal, thereby preventing the urokinase-type plasminogen activator from converting plasminogen into plasmin. DNA fragments which encode for soluble, active fragments of the urokinase-type plasminogen activator are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 16 OF 17 MEDLINE

ACCESSION NUMBER: 1998364972 MEDLINE
DOCUMENT NUMBER: 98364972 PubMed ID: 9701242
TITLE: **Thrombin receptor** overexpression in malignant and physiological invasion processes.
AUTHOR: Even-Ram S; Uziely B; Cohen P; Grisaru-Granovsky S; Maoz M; Ginzburg Y; Reich R; Vlodavsky I; Bar-Shavit R
CORPORATE SOURCE: Department of Oncology, Hadassah-Hebrew University Hospital, Jerusalem, Israel.
SOURCE: NATURE MEDICINE, (1998 Aug) 4 (8) 909-14. Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980903
Last Updated on STN: 19980903
Entered Medline: 19980825

AB Although the involvement of soluble and matrix-immobilized proteases in tumor cell invasion and metastasis is well recognized, the role of proteolytically activated cell surface receptors has not been elucidated. We report here that **thrombin receptor**, a member of the protease-activated receptor family, is preferentially expressed in highly metastatic human breast carcinoma cell lines and breast carcinoma biopsy specimens. Introduction of **thrombin receptor** **antisense** cDNA considerably inhibited the invasion of metastatic breast carcinoma cells in culture through a reconstituted basement membrane. During placental **implantation** of the human embryo, **thrombin receptor** is transiently expressed in the invading cytotrophoblasts. These results emphasize the involvement of **thrombin receptor** in cell invasion associated with tumor progression and normal embryonic development.

L16 ANSWER 17 OF 17 USPATFULL

ACCESSION NUMBER: 96:43770 USPATFULL
TITLE: Urokinase-type plasminogen activator receptor antibodies
INVENTOR(S): Dano, Keld, Charlottenlund, Denmark
Ronne, Ebbe, Copenhagen, Denmark
Behrendt, Niels, Bagsvaerd, Denmark
Ellis, Vincent, Copenhagen, Denmark
Hoyer-Hansen, Gunilla, Gentofte, Denmark
Pyke, Charles, Soborg, Denmark
Bruenner, Nils, Virum, Denmark
PATENT ASSIGNEE(S): Cancerforskningsfondet af 1989, Copenhagen, Denmark (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5519120		19960521
APPLICATION INFO.:	US 1993-85122		19930617 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1991-824189, filed on 6 Dec 1991, now abandoned which is a		

continuation-in-part of Ser. No. US 1989-374854, filed on 3 Jul 1989, now abandoned which is a continuation-in-part of Ser. No. US 1989-334613, filed on 7 Apr 1989, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Feisee, Lila
ASSISTANT EXAMINER: Loring, Susan A.
LEGAL REPRESENTATIVE: Cooper, Iver P.
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 61 Drawing Figure(s); 35 Drawing Page(s)
LINE COUNT: 5458
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A monoclonal or polyclonal antibody directed against urokinase plasminogen activator receptor (u-PAR), or a subsequence, analogue or glycosylation variant thereof. Antibodies are disclosed which react with free u-PAR or with complexes between u-PA and u-PAR and which are capable of 1) catching u-PAR in ELISA, or 2) detecting u-PAR, e.g. in blotting, or 3) in radioimmunoprecipitation assay precipitate purified u-PAR in intact or fragment form, or 4) is useful for immunohistochemical detection of u-PAR, e.g. in immunostaining of cancer cells, such as in tissue sections at the invasive front, or 5) inhibits the binding of pro-u-PA and active u-PA and thereby inhibits cell surface plasminogen activation. Methods are disclosed 1) for detecting or quantifying u-PAR, 2) for targeting a diagnostic to a cell containing a u-PAR on the surface, 3) for preventing or counteracting proteolytic activity in a mammal. Methods for for selecting a substance suitable for inhibiting u-PA/u-PAR interaction, for preventing or counteracting localized proteolytical activity in a mammal, for inhibiting the invasion and/or metastasis comprise the use of the antibodies and of nude mice inoculated with human cancer cells which are known to invade and/or metastasize in mice and having a distinct color, f.x. obtained by means of an enzyme and a chromogenic substrate for the enzyme, the color being different from the cells of the mouse.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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Executing the logoff script...

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	321.20	321.41

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-4.96	-4.96

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 14:33:41 ON 04 DEC 2002